INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/07748

A. CLASSIFICATION OF SUBJECT MATTER								
IPC(8) : C12Q 1/68; C07H 21/04								
US CL	: 435/6; 536/23.1, 23.5 International Patent Classification (IPC) or to both nati	onal classification and IPC						
B. FIELD	S SEARCHED							
	cumentation searched (classification system followed by	y classification symbols)						
Minimum doc	5/6; 536/23.1, 23.5							
0.3 43.	5/ 0, 55 0/ 25. 2, 25. 5							
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched								
Electronic dat Please See Co	Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet							
C. DOCI	JMENTS CONSIDERED TO BE RELEVANT		D. Lawrette alaim No.					
Category *	Citation of document, with indication, where ap	propriate, of the relevant passages	Relevant to claim No.					
X	US 5,776,683 A (SMITH et al) 07 July 1998 (07.07.1	1998), especially col. 6, 25 and Table 7.	1-4					
Y	SQUIRE et al. High-resolution mapping of amplifications of common by use of CGH analysis of cDNA micro Cancer. 2003, Vol. 38, pages 215-225, especially pages 215-225.	1-4						
Evethor	r documents are listed in the continuation of Box C.	See patent family annex.						
 	Special categories of cited documents:	"I" later document published after the inten- and not in conflict with the application	national filing date or priority date out cited to understand the					
	t defining the general state of the art which is not considered to be of	principle or theory underlying the inven	tion					
particular	oplication or patent published on or after the international filing date	document of particular relevance; the cleansidered novel or cannot be considered to the document is taken alone	aimed invention cannot be ed to involve an inventive step					
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"O" documen	it referring to an oral disclosure, use, exhibition or other means		amily					
priority o	nt published prior to the international filing date but later than the date claimed	"&" document member of the sarrie patent f						
	actual completion of the international search	Date of mailing of the international search 21 FEB: 200						
	18 January 2006 (18.01.2006) Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Authorized officer Carla Myers							
Me Co	ommissioner for Patents	Carra Mayoro	the for					
Al	O. Box 1450 exandria, Virginia 22313-1450 fo. (571) 273-3201	Telephone No. 571-272-1600						

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/07748

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons: Claims Nos.:	Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)						
because they relate to subject matter not required to be scarched by this Authority, namely. 2. Claims Nos.:	This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:						
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically. 3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet) This International Searching Authority found multiple inventions in this international application, as follows: Please See Continuation Sheet 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims. 2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees. 3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-4, with respect to the amplicon comprising chromosome 8q24.13 Remark on Protest	1.						
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheef) This International Searching Authority found multiple inventions in this international application, as follows: Please See Continuation Sheet As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: No required additional search fees were timely paid by the applicant. Consequently, this international search report covers only those claims for which fees were paid, specifically claims Nos.: No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-4, with respect to the amplicon comprising chromosome 8q24.13 Remark on Protest The additional search fees were accompanied by the applicant's protest and, where applicable, the	2.	because they relate to parts of the international application that do not comply with the prescribed requirements to such					
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	4.	restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-4, with respect to the amplicon					
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The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.							

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BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional examination fees must be paid.

Groups 1-47, claims 1-4 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing one of the 47 amplicons set forth in Table 2. For example, Group 1 is drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing the 5.3 MB amplicon comprising chromosome 8q24.13. Upon election of one of the groups, please specify the amplicon to be searched.

Groups 48-3097, claims 5-9 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing one of the sequences of SEQ ID NO: 1-3049 and assaying for a change in the level of expression of one of the sequences. For example, Group 48 is drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing SEQ ID NO: 1. Upon election of one of the groups, please specify the SEQ ID NO of the elected

Groups 3098-6147, claims 10-11 (in part), drawn to methods for identifying a cancerous state of a cell by assaying for the sequence of one of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

Groups 6148-9196, claims 12-34 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049 and assaying for a change in the activity of the polypeptide. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched. Further, it is noted that claim 23 has been included with this grouping because it appears that claim 23 intends to depend from claim 15, rather than claim 11.

Groups 9197-12,245, claims 35-39 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing one of the sequences of SEQ ID NO: 1-3049 and assaying for a change in the cancer cell growth of said cell. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

Groups 12,246-15,294, claims 40-47 (in part), drawn to methods for treating cancer by using a compound that effects the activity of a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the corresponding SEQ ID NO of the elected group to be searched.

group to be searched.

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Groups 15295-18343, claims 48-55 and 57-60 (in part), drawn to methods for monitoring the progress of a cancer therapy by assaying for the level of a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

Groups 18,344-21,392, claim 56 (in part), drawn to methods for producing data comprising producing test data sufficient to identify the chemical nature of a test compound that effects the activity of a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

The inventions listed as Groups 1-21,392 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

In accordance with 37 CFR 1.475(d) Applicant is entitled to an examination of the first product, method of making said product and method of using said product. In the instant case, the first method is one which requires one of the 47 amplicons of Table 2. This product is not required for the methods set forth in the remaining groups. Thereby, Groups 48-21,392 constitute distinct groups which do not share the same corresponding technical feature of groups 1-47. Further, unity of invention exists only when there is a technical relationship among those inventions involving one or more of the same or corresponding technical features. The expression 'special technical feature' means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. The technical feature linking the claims 5-60 is the HAS2 gene. However, the HAS2 gene was known in the art at the time the invention was and thereby does not constitute a contribution over the prior art (see NCBI Database, GenBank Accession No. U54804). Accordingly, there is no special technical feature linking the recited groups, as would be necessary to fulfill the requirement for unity of invention.

It is also noted that each of the present claims has been presented in improper Markush format, as distinct methods are improperly joined in the claims. Each amplicon of Table 2 and each nucleic acid sequence of SEQ ID NO: 1-3049 is structurally and functionally distinct from and has a different special technical feature than each other the amplicons and nucleic acid sequences. The chemical structure of each amplicon and nucleic acid sequence differ

from each other. For example, a polynucleotide comprising SEQ ID NO: 1 is chemically, structurally, and functionally different from a molecule comprising SEQ ID NO: 2. Given the differences in the structure, function and effect the amplicons of Table 2 and the sequences of SEQ ID NO: 1-3049, these compounds are not considered to share a special technical feature as would be necessary to fulfill the requirement for unity of invention. These distinct compounds do not have both a "common property or activity" and a common structure as would be required to show that the inventions are "of a similar nature." As the products and methods encompassed by the claims do not share a special technical feature, the distinct products and methods may not properly be presented in the alternative. Accordingly, the claims have been separated into a number of groups corresponding to the number of different inventions encompassed by the claims, and the claims will be searched only as they read upon the invention of the elected group

Additionally, each of the claimed methods have different objectives and require different process steps. The methods of claims 1-4 require cells containing one of the amplicons of Table 2 and requires assaying for a change in the amplification ratio of the amplicon. The methods of claims 5-9 require the use cells that contain one of the sequences of SEQ ID NO: 1-3049, and requires assaying for a change in gene expression by assaying for mRNA or protein levels in order to

accomplish the objective of identifying a antineoplastic agent. The methods of claims 10-11 require assaying for the level of one of the sequences of SEQ ID NO: 1-3049 in order to accomplish the objective of identifying a cancerous state of a cell. The methods of claims 12-34

require contacting a cell with a test agent and assaying for a change in biological activity of a polypeptide encoded by SEQ ID NO: 1-3049. The methods of claims 35-39 require contacting a cell with a test compound and assaying for the cancerous state of a cell. The methods of

claims 40-47 require administering an agent to an individual in order to accomplish the objective of treating cancer. The methods of claims 48-55 and 57-60 require determining gene expression levels of a polypeptide of one of SEQ ID NO: 1-3049 and assaying for polypeptide levels in order to accomplish the objective of monitoring the progress of cancer therapy. The method of claim 56 requires identifying test compounds that have

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antineoplastic activity and producing test data in order of the test compound. In addition to differences in ordering of the present Groups are not directed to the same or common special technical feature, for the respective of the same of the same or common special technical feature.	ler to obtain sufficient data to identify the chemical structure bjectives, effects, and method steps, it is again noted that the detection or identification of molecules having the easons discussed above.
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Continuation of B. FIELDS SEARCHED Item 3: WEST: USPT, JPAB, EPAB, DWPI, PGPUB; DIALOG: MED search terms: 8q24.13, 8q24.1; amplification or amplified or continuation of B. FIELDS SEARCHED Item 3:	LINE, CA, BIOSIS, EMBASE opy number; cancer or tumor or neoplasm

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Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

Published:

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- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DETERMINING CANCER-LINKED GENES AND THERAPEUTIC TARGETS USING MOLECULAR CYTOGENETIC METHODS

(57) Abstract: Methods for identifying antineoplastic agents by using their ability to modify expression of specific genes or the biological activity of polypeptides encoded by such genes, wherein said genes are located in specific chromosomal regions, called amplicons, or regions of interest, and the presence of such amplified regions within a cancerous cell, are disclosed. Also described are methods for diagnosing cancerous, or potentially cancerous, conditions using these methods. Also encompassed are methods involving determining the modulated expression of the genes in these regions of interest (ROIs), or amplicons, as pharmacodynamic/pharmacogenetic/surrogate markers and/or for patient profiling prior to accrual for clinical trials/treatments based on the identification of these genes as validated gene/drug targets in various cancer tissue types.

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DETERMINING CANCER-LINKED GENES AND THERAPEUTIC TARGETS USING MOLECULAR CYTOGENETIC METHODS

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This application claims priority of U.S. Provisional Application Serial No. 60/550,304, filed 8 March 2004, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

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The present invention relates to Identification of amplifications / gains of genomic segments of DNA within human chromosomes in diseased states, such as cancer, that are demarcated and limited within specific chromosomal bands and defined herein as "amplicons" and whose disruption and/or change in expression is useful to distinguish cancerous from non-cancerous tissue and serve as potential therapeutic targets, pharmacodynamic /pharmacogenetic/surrogate and prognostic and diagnostic markers.

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BACKGROUND OF THE INVENTION

Malignant tumors are a leading cause of death in the United States and one in four Americans is likely to die of cancer. This disease is often characterized by an increase in the number of abnormal, neoplastic cells that are ultimately derived from a normal tissue after which the cells proliferate to form a tumor, which can then metastasize (spreading into adjacent tissues or traveling elsewhere in the body via the bloodstream or lymphatic system).

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The genomes of various well-studied tumors carry several different independently altered genes, including activated oncogenes and inactivated tumor suppressor genes. Chromosomal abnormalities have been identified in most cancer cells. Conventional chromosome banding techniques allow for the detection of specific chromosomal defects in tumor cells but interpretation of the banding pattern is sometimes difficult, particularly when complex chromosomal rearrangements or subtle abnormalities are present. In recent years, new techniques, such as CGH and SKY, based on fluorescent in situ hybridization (FISH) (Pinkel et al., Proc Nat Acad Sci USA 85:9138-42 (1988)) been developed to overcome the limitations of conventional chromosome banding. CGH measures intensities of fluorescently labeled tumor DNA and normal DNA following hybridization to normal chromosomes (Kallioniemi et al., Science 258:818-21 (1992)). Gain or loss of copy number of a particular chromosome or chromosome region in the tumor DNA is determined by the relative intensity of a fluorescence ratio. SKY utilizes a cocktail of chromosome probes, fluorescently labeled to specify each chromosome, which is hybridized to tumor chromosomes in an effort to identify numerical and structural abnormalities in the tumor cell (Schröck et al., Science 273:494-7 (1996)). CGH and SKY have been used to identify chromosomal regions that harbor genes significant to the process of tumor initiation or progression.

The identification of amplifications of genomic DNA within well defined and demarcated limits on human chromosomes is done at a resolution of human chromosome banding limited to 400-550 bands by the technique of Comparative Genomic Hybridization (CGH). The present invention applies custom protocols to obtain human template chromosomes that are resolved to 850 to 1000 band resolution of human chromosomes (ISCN, 1985), to perform CGH on a large number of cell lines/ tissue samples/tumor cells. This allows the identification of regions of genomic DNA amplifications ranging from 2-5 Mbp at the highest limits of resolution of human chromosomes, detected by fluorescent intensity evaluations performed at the microscope.

Amplicons, or regions of interest,, from 10-20 Mb and more are also defined by these methods. These amplicons contain a gene, or genes, that are amplified (meaning copy number gains), and/or differentially expressed in the tissue/ cells of origin. Genes identified as being amplified and/or over-expressed provide targets for intervention with a small molecular therapeutic, antibodies, anti-sense or other therapeutic modalities. A gene or genes within these regions could also be used for diagnostic or prognostic molecular pathology characterization and useful as pharmacodynamic biomarkers for drug response profiling and patient sub-set selection and stratification.

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BRIEF SUMMARY OF THE INVENTION

In one aspect the present invention relates to a set of genes that have been localized within human chromosomal regions of interest (ROI) that have been identified by molecular cytogenetic techniques. In particular, the present invention relates to chromosomal regions of interest, or amplicons, that are summarized in Table 1 and containing genes corresponding to cDNA sequences shown in the sequence listing described herein.

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In another aspect, the present invention relates to a method for diagnosing the presence of a cancerous condition, or diagnosing a predisposition to developing a cancerous condition, in an animal, especially a human being, by determining the amplification and/or over-expression, of one or more genes corresponding to SEQ ID NO: 1-3049 in a cell, or tissue sample, obtained from an animal. The animal may be afflicted with, or at risk of developing, such a cancerous condition, or otherwise predisposed to develop such a condition.

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In a further aspect, the present invention relates to a method for the treatment of a cancerous condition, especially one involving breast, colon, lung, cervix, kidney, pancreas and prostate tissues, utilizing selected chemical

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agents having anti-tumor activity as identified using one of the assays disclosed herein.

Thus, in one aspect the present invention relates to a method for identifying an antineoplastic agent, comprising:

- (a) contacting a test compound with a cell that expresses at least one gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 - 3049 and under conditions promoting expression of said gene; and
- (b) determining a change in expression of said gene as a result of said contacting 10

wherein a change in expression indicates gene modulation thereby identifying said test compound as a gene modulating agent. In a preferred embodiment thereof, the change in expression is a decrease in expression.

In a further aspect, the present invention relates to a method for 15 identifying a compound as an anti-neoplastic agent, comprising:

- (a) contacting a test compound with a polypeptide encoded by a gene selected from SEQ ID NO: 1 - 3049,
- (b) determining a change in a biological activity of said polypeptide due to said contacting,

wherein a change in activity indicates anti-neoplastic activity and thereby identifies such test compound as an agent having antineoplastic activity.

Preferably, the change in biological activity is a decrease in biological activity. Also preferred is where the biological activity is an enzyme activity, most preferably involving an enzyme selected from kinase, protease, peptidase, phosphodiesterase, phosphatase, dehydrogenase, reductase, carboxylase. transferase, deacetylase and polymerase. Also preferred is a biological activity that is a membrane transport activity, an integrin, a 30 Cytochrome P450 enzyme, a nuclear hormone receptor, or a receptor activity, such as a G-protein-coupled receptor. In other preferred embodiments, the polypeptide is contained in a cell.

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The present invention also relates to a method for treating cancer comprising contacting a cancerous cell with an agent first identified as having gene modulating activity using any of the methods of the invention and in an amount effective to cause a reduction in cancerous activity of said cell. In a preferred embodiment, said cancerous cell is contacted *in vivo*, as where the agent is administered to a mammal, especially a human being, afflicted with cancer and in an amount sufficient to ameliorate the cancer.

The present invention further relates to a method for treating cancer comprising contacting a cancerous cell with an agent having affinity for an expression product of a gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 – 3049 and in an amount effective to cause a reduction in cancerous activity of said cell. Preferably, the expression product is a polypeptide and the agent is an antibody.

The present invention also relates to a method for monitoring the progress of cancer therapy in a patient comprising monitoring in a patient undergoing cancer therapy the expression of a gene corresponding to a polypeptide having a sequence selected from SEQ ID NO: 1-3049, preferably wherein the gene comprises a sequence of SEQ ID NO: 1-3049, such as where the cancer therapy is chemotherapy.

In a further embodiment, the present invention relates to a method for determining the likelihood of success of cancer therapy in a patient, comprising monitoring in a patient undergoing cancer therapy the expression of a gene corresponding to a polynucleotide having a sequence of one or SEQ ID NO: 1-3049 wherein a decrease in said expression prior to completion of said cancer therapy is indicative of a likelihood of success of said cancer

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therapy, preferably wherein the gene comprises a sequence of SEQ ID NO: 1-3049 and wherein the cancer therapy is chemotherapy.

The present invention still further relates to a method for determining the progress of a treatment for cancer in a patient afflicted therewith, following commencement of a cancer treatment on said patient, comprising:

- (a) determining in said patient a change in expression of one or more genes corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 3049; and
- (b) determining a change in expression of said gene compared to expression of said one or more determined genes prior to commencement of said cancer treatment;

wherein said change in expression indicates progress of said treatment thereby determining the progress of said treatment. Preferred embodiments include where the change in expression is a decrease in expression and said decrease indicates success of said treatment.

20 DEFINITIONS

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As used herein, the following terms have the indicated definition unless expressly stated otherwise.

The term "amplicon" refers to regions of interest, i.e., genomic segments of DNA within human chromosomes in diseased states like cancer that are demarcated and limited within specific chromosomal bands. Since these amplicons contain sequences of a gene/ or genes that are amplified (copy number gains), and/ or differentially expressed in the tissue/ cells of origin, a listing of these genes within the amplicons detected are listed in Table 3. Genes identified as being amplified and/or over-expressed within the amplicons provide a useful target for intervention with small/large

molecule/protein/antibody therapeutics, anti-sense or other therapeutic modalities. A gene or genes within these regions is also useful for diagnostic or prognostic molecular pathology characterization/companion diagnostics, and useful as pharmacodynamic biomarkers for drug response profiling and patient sub-set selection and stratification.

The term "percent identity" or "percent identical," when referring to a sequence, means that a sequence is compared to a claimed or described sequence after alignment of the sequence to be compared (the "Compared Sequence") with the described or claimed sequence (the "Reference Sequence"). The Percent Identity is then determined according to the following formula:

Percent Identity = 100 [1-(C/R)]

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wherein C is the number of differences between the Reference Sequence and the Compared Sequence over the length of alignment between the Reference Sequence and the Compared Sequence wherein (i) each base or amino acid in the Reference Sequence that does not have a corresponding aligned base or amino acid in the Compared Sequence and (ii) each gap in the Reference Sequence and (iii) each aligned base or amino acid in the Reference Sequence that is different from an aligned base or amino acid in the Compared Sequence, constitutes a difference; and R is the number of bases or amino acids in the Reference Sequence over the length of the alignment with the Compared Sequence with any gap created in the Reference Sequence also being counted as a base or amino acid.

If an alignment exists between the Compared Sequence and the Reference Sequence for which the percent identity as calculated above is about equal to or greater than a specified minimum Percent Identity then the Compared Sequence has the specified minimum percent identity to the Reference Sequence even though alignments may exist in which the

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hereinabove calculated Percent Identity is less than the specified Percent Identity.

As used herein, the terms "portion," "segment," and "fragment," when used in relation to polypeptides, refer to a continuous sequence of residues, such as amino acid residues, which sequence forms a subset of a larger sequence. For example, if a polypeptide were subjected to treatment with any of the common endopeptidases, such as trypsin or chymotrypsin, the oligopeptides resulting from such treatment would represent portions, segments or fragments of the starting polypeptide. When used in relation to a polynucleotide, such terms refer to the products produced by treatment of said polynucleotides with any of the common endonucleases, or any stretch of polynucleotides that could be synthetically synthesized.

As used herein, the term "DNA segment" or "DNA sequence" refers to a DNA polymer, in the form of a separate fragment or as a component of a larger DNA construct, which has been derived from DNA, and may include both single stranded and duplex sequences. Such segments are provided in the form of an open reading frame uninterrupted by internal non-translated sequences, or introns, which are typically present in eukaryotic genes.

The term "coding region" refers to that portion of a gene which either naturally or normally codes for the expression product of that gene in its natural genomic environment, i.e., the region coding *in vivo* for the native expression product of the gene.

The term "nucleotide sequence" refers to a heteropolymer of deoxyribonucleotides. Generally, DNA segments encoding the proteins provided by this invention are assembled from cDNA fragments and short oligonucleotide linkers, or from a series of oligonucleotides, to provide a synthetic gene which is capable of being expressed in a recombinant

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transcriptional unit comprising regulatory elements de rived from a microbial or viral operon.

The term "expression product" means that polypeptide or protein that is the natural translation product of the gene and any nucleic acid sequence coding equivalents resulting from genetic code degeneracy and thus coding for the same amino acid(s).

The term "fragment," when referring to a coding sequence, means a portion of DNA comprising less than the complete coding region whose expression product retains essentially the same biological function or activity as the expression product of the complete coding region.

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DETAILED SUMMARY OF THE INVIENTION

The present invention relates to a set of genes that are amplified and/or over-expressed genes in cancer cell lines and have been localized to various chromosomal regions of interest. These genes have been identified through a combination of CGH, SKY, expression analysis and Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR). Such genes are both markers and potential therapeutic targets for cancer, in particular breast; colon, lung and prostate malignancies. In addition, the amplified nature of such genes provides a means of diagnosing a cancerous condition, or predisposition to a cancerous conditions, by determining the amplification of one or more of such genes in a patient afflicted with, or predisposed toward, or otherwise at risk of developing, cancer.

In one aspect the present invention relates to a set of genes that have been localized within human chromosomal regions of interest (ROI) that have been identified by molecular cytogenetic techniques. In particular, the present

invention relates to chromosomal regions of interest, or amplicons, that are summarized in Table 1. Table 2 lists tissues where the amplicons are found, cell lines expressing them, the amplification ratios found in those tissues for cancer versus normal cells, amplicon size and the chromosomal locations of the amplicons. Table 3 lists the chromosomal locations and accession number identifications of these regions of interest and which serve to correlate amplicons with the cDNA sequences of SEQ ID NO: 1-3049.

10 Table 1 - List of Amplicons

	AMPLICON	CHR	BPSTART	BPEND	BPLENGTH
15 20	A1 A2 A3 A4 A5 A6 A7	8 13 5 13 7 10 7	122000000 96500000 175000000 26500000 101000000 73500000 71000000	127500000 100000000 181500000 34000000 106000000 82500000 77500000	5500000 3500000 6500000 5000000 9000000 6500000
	A8 A9 A10 A11	1 6 18 9	116500000 36000000 70500000 9000000	120000000 41000000 76500000 18500000	3500000 5000000 6000000 9500000

For Table 1, CHR means chromosome number, BPLENGTH represents the number of nucleotides in the amplicon. BPSTART refers to "base pair start point" and BPEND refers to "base pair end point" along the chromosome based on the July 2003 human reference sequence UCSC version hg16 (NCBI Build 34).

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Table 2. Amplicon Locations

** **	A	ticoup	chrom	band	band		amplicon
cell line	Amp #	tissue	CHIOHI	start	stop	Ratio	size_MB_
11001054	- #	Breast	8	q24.13	q24.13	14	5.3
HCC1954 NCI_H446	A1	scLung	8	q24.13	q24.21	8	8.3
NCI_H440 NCI_H827	A1	scLung	8	q24.13	q24.21	6	8.3
HCC202	A1	Breast	8	q24.13	q24.21	6	8.3
NCI_H82	A1	scLung	8	q24.13	q24.13	7	5.3
NCI_H23	A1	nscLung	8	q24.13	q24.13	7	5.3
MDA MB436	A2	Breast	13	g32.2	q32.3	6	5.3
NCI_H1963	A2	scLung	13	q32.3	q32.3	6	3.3
EFM192A	A2	Breast	13	q32.3	q34	8	18.8
MDA MB157	A2	Breast	13	q32.3	q34	5	18.8
HCC1937	A2	Breast	13	q32.3	q32.3	4	3.3
SKBR3	A2	Breast	13	q32.3	q32.3	4	18.8
NCI_H1963	A2	nscLung	13	q32.3	q32.3	6	3.3
HCC1954	A3	Breast	5	q35.3	q35.3	4	4.3
MDA MB436	A3	Breast	5	q35.1	q35.3	7	14
BT20	A4	Breast	5	q35.1	q35.3	4	14
KPL1	A5	Breast	5	q35.1	q35.3	4	14
HCC3153	A6	Breast	5	q35.3	q35.3	3	4.3
HT29	A4	Colon	13	q12.3	q13.2	5	9
SW403	A4	Colon	13	q21.1	q21.2	15	6
BT20	A4	Breast	13	q12.3	q13.2	4	9
CPDR9	A4	Prostate	13	q12.2	q12.3	2	7.1
SW480	A5	Colón	7	q22.2	q22.2	9	1
X71	A5	Colon	7	q22.1	q22.2	5	7.2
X72	A5	Colon	7	q22.3	q22.3	6	3.3
Lovo	A6	Colon	7	q22.1	q22.2	5	7.2
X1819_1	A7	Colon	7	q22.1	q22.2	5	7.2
EFM19	A6	Breast	10	q22.1	q22.3	6	15.3
PC3	A6	Prostate	10	q22.2	q22.3	7	8.3 40.7
MDA_MB436	A6	Breast	10	q22.1	q22.2	3	10.7 8.3
SKBR3	A6	Breast	10	q22.2	q22.3	4	15.3
SW48	A6	Colon	10	q22.1	q22.3	4	8.3
X71	A6	Colon	10	q22.2	q22.3	2	4
SKBR3	A 7	Breast	7	q11.23	q11.23		4
X72	A7	Colon	7	q11.23	<u>-</u>		4
X71	A7	Colon	7	q11.23			4
X1819_1	A7	Colon	7	q11.23			4
NCI_H69	A7	scLung	/	q11.23			9
BT20	A8	Breast	7	p12.2	p13.2 p12	6	6.7
CAMA-1	A8	Breast	1	p12	p12.3		14.7
KPL-1	A8	Breast	7	p11.2	p13.3 p21.2		3.4
Colo205	A9	Colon	6	p21.2	p21.2 p21.2		9.8
MDA_MB231	A9	Breast	6	p21.1	pz 1.2	•	3.0

NCIH522 PANC-1 NCI_H1607 NCI_H446	A9 A10 A11 A11	nscLung Pancreas scLung scLung	6 18 9	p21.2 q23 p22.2 p22.3	p21.31 q23 p23 p22.3	6 7 10 8	9.1 5.2 14.5 2.9
HCC1954	A11	Breast	9	p22.2	p23	10	14.5

In addition, SEQ ID NO: 1-3049 represents the nucleotide sequences for cDNA sequences corresponding to genes located in these regions of interest. Such regions contain genes found to be amplified and over-expressed in cancerous tissues, especially of breast, colon, lung, cervix, kidney, pancreas and prostate.

Each amplicon may contain about 75 genes, at least one of which will be amplified in a cancerous condition. Genes that show amplification and/or over-expression can be indicative of the cancerous status of a given cell.

Briefly, the procedures used to identify the genes disclosed herein may be summarized as follows:

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For CGH analysis, based on detailed molecular cytogenetic characterizations, the following data sets are generated, which may include regions reported in the public domain as well as unique regions not previously known.

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1. A map of chromosomal regions involved in consistent, recurrent and high level genomic gains (i.e., amplifications) for a representative cancer cell line or tumor type (e.g. colon, prostate, breast and lung) that can be recognized as a pattern/signature for a given tumor type.

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- 2. A map of chromosomal regions containing genomic losses (i.e., deletions) in each tumor type and individual cell line to be examined.
- 3. Levels of intensities of gains and losses categorized for entry into a database.

4. A comparison of the patterns of gains and losses between the clinical samples (e.g. colon xenografts) and cell lines (e.g., colon) of matched Stages and Grades.

5. A comparison of the patterns of gains and losses between primary prostate tumor cell lines (e.g., CPDR lines) and metastatic prostate tumor cell lines (e.g., DU 145, PC3 and LNCaP).

In accordance with the present invention, for SKY analysis, data sets were generated according to the following steps:

- 1. Identification and development of a database of novel chromosomal rearrangements in epithelial cancer cell lines.
- 2. Identification of novel translocations involving specific chromosomes or chromosomal regions
- 3. Reconciliation of SKY and CGH analysis on the same cell line as a verification of the combined findings.

Combining genomic DNA analysis of gains and losses in the tumor cell lines/clinical samples with cDNA expression analysis from matched tumor types displayed ordered on the assembled Human genome sequence :

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1. A pattern of gene expression on a Affymetrix chip set (U95 and U133) was used to generate differential gene expression profiles between samples sets containing normal and malignant tissues from colon, prostate, lung, breast and various cell lines.

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2. A Spotfire™ visualization tool was developed that allowed the generation of a list of all the genes that are present in the Human genome sequence within the defined regions of gains/losses for each cell type/tumor type to identify genes to include in the HITS platform and for identification of cancer associated genes

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3. The following algorithm was employed:

i) Match chromosomal regions of amplification/gains defined by CGH with the location of genes/ESTs on an Affymetrix chip as mapped to a Human genome template.

ii) Identify genes/ESTs over-expressed in tumor tissue compared to normal tissue in said chromosomal regions using.

(iii) Compile data on cell lines of a particular tumor type and different tumor types showing clusters of genomic gains and losses at certain chromosomal regions.

iv) Pick BACs that span the chromosomal regions consistently gained and containing over-expressed genes in an effort to positionally clone novel cancer genes (oncogenes and genes in relevant pathways)

v) Validate the identified genes by
A) Picking STS markers that identify the gene sequence and quantify the relative copy number in genomic DNA and RNA across a panel of tumor cell lines.

B) Develop probes for FISH on chromosomes from tumor cell lines and primary tumor tissue micro-arrays.

4. The expression data from tumor cell lines that have undergone SKY/CGH analysis was used to pick candidate genes to validate as individual targets in functional genomic assays and in-vivo assays and for use in the transcriptional assay platform.

In accordance with the present invention, over-expression of cellular genes is conveniently monitored in model cellular systems using cell lines (such as is used in the example below), primary cells, or tissue samples maintained in growth media. For different purposes, these may be treated with compounds at one or more different concentrations to assay for modulating agents. Thus, cellular RNAs are isolated from the cells or cultures as an indicator of selected gene expression. The cellular RNAs are then divided and

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subjected to analysis to determine the presence and/or quantity of specific RNA transcripts, which transcripts are then amplified for detection purposes using standard methodologies, such as reverse transcriptase polymerase chain reaction (RT-PCR). The levels of specific RNA transcripts, including their presence or absence, are determined. When used for identification of modulating agents, such as anti-neoplastic agents, a metric is derived for the type and degree of response of the treated sample compared to control samples.

In accordance with the foregoing, the amplicons identified as being amplified and/or over-expressed, which can include increased copy number thereof, in cancerous cells are localized in chromosomal regions of interest as identified in Tables 2 and 3.

The genes localized in these amplicons may be utilized to characterize, the cancerous, or non-cancerous, status of cells, or tissues. The methods of the invention may be used with a variety of cell lines or with primary samples from tumors maintained *in vitro* under suitable culture conditions for varying periods of time, or *in situ* in suitable animal models.

The amplicons disclosed herein are expressed at levels in cancer cells that are different from the expression levels in non-cancer cells. Expression in cancer versus non-cancer cells of the same tissue type is a key identifier.

In accordance with the forgoing, the present invention also relates to a method for identifying a gene modulating agent, such as an anti-neoplastic agent, comprising:

(a) contacting a test compound, a compound whose gene-modulating and/or anti-neoplastic activity is to be determined, with one or more cells expressing one or more genes mapped to the chromosomal region of interest, or amplicon, for genes as identified in Table 3, and

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compared to when said contacting has not occurred,

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wherein a change in expression of said gene is indicative of gene modulating activity, thereby identifying said test compound as a gene modulating agent.

In accordance with the foregoing, the present invention relates to a method for identifying an antineoplastic agent, comprising:

- (a) contacting a test compound with a cell that expresses one or more amplicons of Table 2 having an amplification ratio of at least 2.0; and
- (b) determining a change in said amplification ratio due to said contacting;

wherein a change in said amplification ratio due to said contacting indicates that said test compound has gene modulating activity

thereby identifying said test compound as a gene modulating agent.

The present invention also contemplates a method for identifying an antineoplastic agent, comprising:

- (a) contacting a test compound with a cell that expresses at least one gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 - 3049 and under conditions promoting expression of said gene; and
- (b) determining a change in expression of said gene as a result of said contacting

wherein a change in expression indicates gene modulation thereby identifying said test compound as a gene modulating agent.

In preferred embodiments of these methods, the change in expression is a decrease in expression and/or the decrease in expression is a decrease in copy number of the gene and/or the gene comprises a nucleotide sequence of one of SEQ ID NO: 1 - 3049 and/or the cell was genetically engineered to express said gene.

Because the genes disclosed herein are over-expressed and relate to the cancerous condition of a cell, successful anti-neoplastic activity will commonly be exhibited by agents that reduce the expression of said genes In one embodiment thereof, the change in expression is a decrease in copy number of the gene or genes under study. In accordance therewith, said change in gene copy number is conveniently determined by detecting a change in expression of messenger RNA encoded by said gene sequence. In another preferred embodiment, expression is determined for more than one such gene, such as 2, 5, 10 or more of the genes.

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Thus, the present invention also encompasses a method for detecting the cancerous status of a cell, comprising detecting elevated expression in said cell of at least one gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 – 3049 whereby such elevated expression is indicative of cancerous status of the cell. In preferred embodiments thereof, the elevated expression is an elevated copy number of the gene.

Other methods useful in measuring a change in expression of the genes disclosed herein include measuring a change in the amount or rate of synthesis of a polypeptide encoded by said gene, preferably a decrease in synthesis of said polypeptide. Most preferably, the polypeptide comprises an amino acid sequence highly homologous to a sequence encoded by a gene mapping to an amplicon disclosed herein and whose expression is elevated in cancer.

The methods of the invention can thus be utilized to identify antineoplastic agents useful in treatment of cancerous conditions. Such activity can be further modified by first identifying such an agent using an assay as already described and further contacting such agent with a cancerous cell, followed by monitoring of the status of said cell, or cells. A change in status indicative of successful anti-neoplastic activity may include a decrease in the rate of replication of the cancerous cell(s), a decrease in the total number of progeny cells that can be produced by said cancerous cell(s), or a decrease in the number of times said cancerous cell(s) can replicate, or the death of said

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cancerous cell(s).

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Anti-neoplastic agents may also be identified using recombinant cells suitably engineered to contain and express the cancer-related genes disclosed herein. In one such embodiment, a recombinant cell is formed using standard technology and then utilized in the assays disclosed herein. Methods of forming such recombinant cells are well known in the literature. See, for example, Sambrook, et al., Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor, N.Y., (1989), Wu et al, *Methods in Gene Biotechnology* (CRC Press, New York, NY, 1997), and *Recombinant Gene Expression Protocols*, in *Methods in Molecular Biology*, Vol. 62, (Tuan, ed., Humana Press, Totowa, NJ, 1997), the disclosures of which are hereby incorporated by reference.

The present invention also relates to a method for detecting the cancerous status of a cell, comprising detecting elevated copy number and/or expression in said cell of at least one gene that maps to a chromosomal region of interest, or amplicon, as identified in Table 3. Such elevated expression may be readily monitored by comparison to that of otherwise normal cells having the same genes. Elevated expression of such genes is indicative of the cancerous state. Such elevated expression, including increased copy number, may be the expression of more than one such gene.

The present invention also relates to a method for detecting a cancerlinked gene comprising the steps of contacting a test compound, identified as having gene modulating activity for a gene mapping to one of the amplicons disclosed herein, with a cell expressing a test gene and detecting modulation, such as decreased activity, of such test gene relative to when said compound

is not present thereby identifying said test gene as a cancer-related gene. In preferred embodiments, the gene determined by said method is an oncogene, or cancer facilitating gene.

In another embodiment, there is provided a method for treating cancer comprising contacting a cancerous cell with an agent first identified as having gene modulating activity using any of the assay methods disclosed according to the invention and in an amount effective to reduce the cancerous activity of said cell. In a preferred embodiment, the cancerous cell is contacted *in vivo*. In other preferred embodiments, said reduction in cancerous activity is a decrease in the rate of proliferation of said cancerous cell, or said reduction in cancerous activity is the death of said cancerous cell.

The present invention further relates to a method for treating cancer comprising contacting a cancerous cell with an agent having activity against an expression product encoded by a gene mapping to an amplicon as disclosed herein, preferably where the expression product is a polypeptide. In a preferred embodiment, said cancerous cell is contacted *in vivo*. In another preferred embodiment, the agent is an antibody.

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Nucleotide sequences mapping to the amplicons disclosed herein may be genomic in nature and thus represent the sequence of an actual gene, such as a human gene, or may be a cDNA sequence derived from a messenger RNA (mRNA) and thus represent contiguous exonic sequences derived from a corresponding genomic sequence or they may be wholly synthetic in origin for purposes of testing. Such cDNA sequences, mapping to the amplicons disclosed herein are identified as SEQ ID NO: 1-3049.

As described in the Example below, the expression of cancer-related genes may be determined from the relative expression levels of the RNA complement of a cancerous cell relative to a normal (i.e., non-cancerous) cell. Because of the processing that may take place in transforming the initial RNA

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transcript into the final mRNA, the sequences disclosed herein may represent less than the full genomic sequence. They may also represent sequences derived from ribosomal and transfer RNAs. Consequently, the genes present in the cell (and representing the genomic sequences) and the sequences disclosed in SEQ ID NO: 1-3049, which are mostly cDNA sequences, may be identical or may be such that the cDNAs contain less than the full genomic sequence. Such genes and cDNA sequences are still considered corresponding sequences because they both encode similar RNA sequences. Thus, by way of non-limiting example only, a gene that encodes an RNA transcript, which is then processed into a shorter mRNA, is deemed to encode both such RNAs and therefore encodes an RNA complementary to (using the usual Watson-Crick complementarity rules), or that would otherwise be encoded by, a cDNA (for example, a sequence as disclosed herein). Thus, the sequences disclosed herein correspond to genes contained in the cancerous or normal cells used to determine relative levels of expression because they represent the same sequences or are complementary to RNAs encoded by these genes. Such genes also include different alleles and splice variants that may occur in the cells used in the methods of the invention.

In addition, sequences encoding the same proteins as any of these genes, regardless of the percent identity of such sequences, are also specifically contemplated by any of the methods of the present invention that rely on any or all of said sequences, regardless of how they are otherwise described or limited. Thus, any such sequences are available for use in carrying out any of the methods disclosed according to the invention. Such sequences also include any open reading frames, as defined herein, present within any genes mapping to the amplicons of the invention.

The present invention also finds use as a means of diagnosing the presence of cancer in a patient, as where a sample of cancerous tissue or cells, or tissues or cells suspected of being cancerous, are examined for elevated expression, such as at least 2 fold expression, of a gene in one of

the amplicons disclosed herein, such as an increased expression of a cDNA sequence, or polypeptide encoded by said cDNA sequence, disclosed in Table 3 and being one of the sequences of SEQ ID NO: 1-3049.

For such purposes, and in accordance with the disclosure elsewhere herein, such diagnosis is based on the detection of elevated expression or amplification, such as elevated copy number, of one or more of the genes identified according to the invention. Such elevated expression can be determined by any of the means described herein.

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In one such embodiment, the elevated expression, as compared to normal cells and/or tissues of the same organ, is determined by measuring the relative rates of transcription of RNA, such as by production of corresponding cDNAs and then analyzing the resulting DNA using probes developed from genes mapping to the amplicons of the invention. Thus, the levels of cDNA produced by use of reverse transcriptase with the full RNA complement of a cell suspected of being cancerous produces a corresponding amount of cDNA that can then be amplified using polymerase chain reaction, or some other means, such as rolling circle amplification, to determine the relative levels of resulting cDNA and, thereby, the relative levels of gene expression.

For RNA analysis, the latter may be isolated from samples in a variety of ways, including lysis and denaturation with a phenolic solution containing a chaotropic agent (e.g., triazol) followed by isopropanol precipitation, ethanol wash, and resuspension in aqueous solution; or lysis and denaturation followed by isolation on solid support, such as a Qiagen resin and reconstitution in aqueous solution; or lysis and denaturation in non-phenolic, aqueous solutions followed by enzymatic conversion of RNA to DNA template copies. Steady state RNA levels for a given type of cell or tissue may have to be ascertained prior to employment of the methods of the invention but such

is well within the skill of those in the art and will not be further described in detail herein.

Alternatively, increased expression, such as increased copy number, may be determined for the genes present in a cancerous cell, or a cell suspected of being cancerous, by determining elevated expression within the regions of interest, or amplicons, disclosed herein. Thus, the DNA of such cells may be extracted and probed for increased gene expression within the area disclosed herein as amplified in different cancer types and tissues.

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In employing the methods of the invention, it should be borne in mind that gene expression indicative of a cancerous state need not be characteristic of every cell found to be cancerous. Thus, the methods disclosed herein are useful for detecting the presence of a cancerous condition within a tissue where less than all cells exhibit the complete pattern of over-expression. For example, a set of selected genes, which are found within the regions of interest disclosed herein, may be found, using appropriate probes, either DNA or RNA, to be present in as little as 60% of cells derived from a sample of tumorous, or malignant, tissue while being absent from as much as 60% of cells derived from corresponding noncancerous, or otherwise normal, tissue (and thus being present in as much as 40% of such normal tissue cells). In a preferred embodiment, such gene pattern is found to be present in at least 70% of cells drawn from a cancerous tissue and absent from at least 70% of a corresponding normal, noncancerous, tissue sample. In an especially preferred embodiment, such gene pattern is found to be present in at least 80% of cells drawn from a cancerous tissue and absent from at least 80% of a corresponding normal, noncancerous, tissue sample. In a most preferred embodiment, such gene pattern is found to be present in at least 90% of cells drawn from a cancerous tissue and absent from at least 90% of a corresponding normal, noncancerous, tissue sample. In an additional embodiment, such gene pattern is found to be present in at least 100% of cells drawn from a cance rous tissue

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and absent from at least 100% of a corresponding normal, non-cancerous, tissue sample, although the latter embodiment may represent a rare occurrence.

Because changes in expression of these genes (up-regulation) are linked to the disease state (i.e. cancer), the change in expression may contribute to the initiation or progression of the disease. For example, if a gene that is up-regulated is an oncogene such a gene provides for a means of screening for small molecule therapeutics beyond screens based upon expression output alone. For example, genes that display up-regulation in cancer and whose elevated expression contributes to initiation or progression of disease represent targets in screens for small molecules that inhibit or block their function. Examples include, but are not be limited to, kinase inhibition, cellular proliferation, substrate analogs that block the active site of protein targets, etc.

It should be noted that there are a variety of different contexts in which genes have been evaluated as being involved in the cancerous process. Thus, some genes may be oncogenes and encode proteins that are directly involved in the cancerous process and thereby promote the occurrence of cancer in an animal. Other genes may simply be involved either directly or indirectly in the cancerous process or condition and may serve in an ancillary capacity with respect to the cancerous state. All such types of genes are deemed with those to be determined in accordance with the invention as disclosed herein. Thus, the gene determined by said method of the invention may be an oncogene, or the gene determined by said method may be a cancer facilitating gene, the latter including a gene that directly or indirectly affects the cancerous process, either in the promotion of a cancerous condition or in facilitating the progress of cancerous growth or otherwise modulating the growth of cancer cells, either in vivo or ex vivo. Such genes may work indirectly where their expression alters the activity of some other gene or gene expression product that is itself directly involved in initiating or

facilitating the progress of a cancerous condition. For example, a gene that encodes a polypeptide, either wild or mutant in type, which polypeptide acts to suppress of tumor suppressor gene, or its expression product, will thereby act indirectly to promote tumor growth.

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Many cancerous genes appear to have their effect by encoding an aberrant protein that functions in a cell in a manner different from that of normal cells, or else said protein is overproduced or underproduced as a result of some mutation in the coding sequence, or promoter or enhancer sequences, of a particular gene, such as one of Genes 1 – 3049 disclosed herein and expressed by the amplicons of the invention.

In accordance with the present invention, there are provided methods for measuring the activity, such as a biological activity, of such a polypeptide. Such biological activity may include any measurable activity, such as chemical reactivity, catalytic ability, binding to specific structures and receptors, acting as a receptor, or just being present in a membrane of a cell and therefore available as a target site for antibodies or other agents. Any such polypeptides may thus provide a target for a chemotherapeutic agent, especially an antineoplastic agent.

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As is well known in the art, polypeptide activities can be measured in different ways so as to enable screening procedures for agents, such as test compounds, that inhibit the activity of the polypeptide and thereby work against the function of that polypeptide, such as where the polypeptide is some type of cancer-related protein, such as that produced by expression of an oncogene, or where the polypeptide is overproduced as part of the cancer initiating or facilitating process. As non-limiting examples, such screening methods for antineoplastic agents can include the measurement of compounds that bind to proteins (or that bind to a gene or a transcript of a gene), compounds that inhibit expression (including processing and/or maturation) of a protein, or the detection of downstream reaction product,

most often with specific antibodies using enzyme-linked immunosorbent assay (ELISA) procedures well known in the art, or compounds that inhibit activity, such as enzyme activity or some other function, or compounds that interact with upstream or downstream proteins (such as with transcription factors or other binding proteins that may serve to regulate gene expression).

In accordance with the foregoing, the present invention relates to a method for identifying a compound as an anti-neoplastic agent, comprising:

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- (a) contacting a test compound with a polypeptide encoded by a gene selected from SEQ ID NO: 1 3049,
 - (b) determining a change in a biological activity of said polypeptide due to said contacting,

wherein a change in activity indicates anti-neoplastic activity and thereby identifies such test compound as an agent having antineoplastic activity.

In a preferred embodiment, the change in biological activity is a decrease in biological activity.

In another preferred embodiment, the biological activity is an enzyme activity, such as where the enzyme is one selected from the group kinase, protease, peptidase, phosphodiesterase, phosphatase, dehydrogenase, reductase, carboxylase. transferase, deacetylase and polymerase.

for such available, as are enzymes 25 for these Assays pharmacologically relevant most (the phosphodiesterases phosphodiesterases are those that hydrolyze cyclic nucleotides (see, for example, cAMP and cGMP assays available from Perkin-Elmer, as well as Estrade et al., Eur. J. Pharmacol. 352:2-3, 157-163 (1998)).

Protein phosphatases remove phosphate residues from proteins. Most tests of their activity use the same assays as for protein kinases. A non-radioactive phosphatase assay system is available from Promega Biotech.

The therapeutically most relevant dehydrogenases oxidize or reduce small molecular weight metabolites, esp. steroid hormones, or that generally use or generate NAD or NADP (see: Haeseleer et al., J. Biol. Chem., 273:21790-21799 (1998)). A commercial assay is available from Cayman Chemical (at www.caymanchem.com).

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Gamma-carboxylases are important enzymes in the blood coagulation process. The main assay protocols use synthetic peptides (see: Ulrich et al., J. Biol. Chem., 263:9697-9702 (1988); Begley et al., J. Biol. Chem., 275:36245-36249 (2000)).

In highly preferred embodiments, the kinase is one of a protein kinase, a serine or threonine kinase, or a receptor tyrosine protein kinase. Where the polypeptide encoded by a gene of the invention is a protein kinase, especially involving tyrosine kinase, various assays for activity are available. Protein kinases add phosphate groups to serine, threonine or tyrosine residues on proteins, most commonly measured with phospho-serine, threonine, or tyrosine-specific antibodies, or generation of radiolabeled substrate, or consumption of ATP, or phosphorylation of (synthetic) small peptides, or measuring downstream enzyme activity and gene transcription. Such assays are commercially available. (See, for example, the tyrosine kinase assay from Roche Molecular Biochemicals). Assays for serine/threonine kinases are also available at Chromagen.com, Upstate Biotechnology, Inc. (Lake Placid, NY, and at upstatebiotech.com) and from Applied BioSystems (Foster City, CA (home.appliedbiosystems.com)).

In other specific embodiments, the protease is a serine protease, cysteine protease or aspartic acid protease, or the transferase is a methyltransferase, preferably a cytosine methyltransferase or an adenine methyltransferase, or the deacetylase is a histone deacetylase, or the

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carboxylase is a γ -carboxylase, or the peptidase is a zinc peptidase, or the polymerase is a DNA polymerase or an RNA polymerase.

Proteases degrade proteins, un-specifically or at specific sites. Almost all pharmacologically relevant ones have very narrowly defined specific substrates, and their activity is most often measured by directly measuring cleavage product or generation of (fluorescent) light after cleavage of synthetic substrates. Assays are available for serine proteases (Calbiochem, Palo Alto, CA, and see Berdichevsky et al., J. Virol. Methods, 107:245-255 (2003), for systeine proteases (See: Schulz et al., Mol. Pathol., 51:222-24 (1998) and Selzer et al., PNAS, 96:11015-11022 (1999)), for aspartic acid proteases (Geno Tech, Inc. at www.genotech.com) and for zinc peptidases (see Evans et al., J. Biol. Chem., 278:23180-23186 (2003)).

Both (regulatory) DNA-methylases and (biosynthetic) protein methylases that are drug targets. (See: Jonassen and Clarke, J. Biol. Chem., 275:12381-12387 (2000); Jackson et al., Nature, 416:556-560 (2002)).

Most HDAC (histone deacetylase) assays use colorimetric or fluorometric (synthetic) substrates. Standard assays are for binding, especially molecular size changes, blocking a specific site, and effects on transcription or downstream reactions (if DNA or RNA is the direct target of a drug). A commercial assay is available from Vinci Biochem (at www.vincibiochem.it).

In another specific embodiment, the biological activity is a membrane transport activity, preferably wherein the polypeptide is a cation channel protein, an anion channel protein, a gated-ion channel protein or an ABC transporter protein. Drug effects on the activity of transporter and channel proteins are screened by measuring increase or decrease of the ((radio-)labeled) transported entity inside or outside the cell, in cell-based assays, ATP consumption (in the case of ATPases), or changes in cell membrane

potential. Assays employing such proteins are available, such as for ABC transporter (see: Marcil et al., Lancet, 354:1341-46 (1999) and for ion channels (from Evotec OAI, at www.evotecoai.com and from PharmaLinks, at www.pharmalinks.org/research/cellsignalling).

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In one embodiment, the polypeptide is an integrin (the signal transduction pathways elicited by the integrins are slow and not very well characterized, hence most assays are either just binding assays or measure downstream biological phenomena (such as migration, invasion, etc.) (See: Ganta et al., Endocrinology, 138:3606-3612 (1997); Sim et al., J. Biomed. Mater. Research, 68A:352-359 (2004); and Weinreb et al., Anal. Biochem., 306:305-313 (2002)), or a Cytochrome P450 enzyme (almost all cytochrome assays require knowledge of what the substrate is and measure conversion of substrate (free or (radio-)labeled) or generation of product; useful C14-labeled Biosciences at Amersham from available substrates are www1.amershambiosciences.com), or a nuclear hormone receptor (Assays available from Discoverx, Fremont, CA, such as an estrogen assay; also see Rosen et al., Curr. Opin. Drug. Discov. Devel., 6:224-30 (2003)).

In one preferred embodiment, the biological activity is a receptor activity, preferably where the receptor is a G-protein-coupled receptor (GPCR).

GPCRs are transmembrane proteins that wind 7 times back and forth through a cell's plasma membrane with a ligand binding site located on the outside of the membrane surface of the cell and the effector site being present inside the cell. These receptors bind GDP and GTP. In response to ligand binding, GPCRs activate signal transduction pathways which induce a number of assayable physiological changes, e.g., an increase in intracellular calcium levels, cyclic-AMP, inositol phosphate turnover, and downstream gene transcription (directly or via reporter-assays) along with other translocation assays available for measuring GPCR activation when the polypeptide

encoded by a gene of the invention is a GPCR. Thus, such proteins work through a second messenger. The result is activation of CREB, a transcription factor that stimulates the production of gene products. One useful assay is the so-called BRET2/arrestin assay, useful in screening for compounds that interact with GPCRs. (See: Bertrand et al, J. Recept. Signal Transduct Res., 22:533-41 (Feb.-Nov. 2002)). In addition, numerous assays are commercially available, such as the Transfluor Assay, available from Norak Biosciences, Inc. (www.norakbio.com) or ArrayScan and KineticScan, both from Cellomics, or assays from CyBio (Jena, Germany).

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Assays useful with the invention are usually set up to screen for agonists or antagonists after adding ligand, but effects on most of these parameters can be measured whether or not the ligand for the receptor is known. Such assays may involve radioligand-binding assays. Activation of the majority of GPCRs by agonists leads to the interaction of beta-arrestin (a protein that is involved in receptor desensitization and sequestration) with the receptor, which is measurable by fluorescence energy transfer

The disclosure of all journal articles, or other publications, referred to herein are hereby incorporated by reference in their entirety.

In one embodiment, the polypeptide is in a solution or suspension and contact with the test compound is by direct contact between the test compound and the protein molecule. Alternatively, the polypeptide may be in a cell and the test compound may have to diffuse into the cell in order to contact the polypeptide. In an alternative embodiment, the test compound may be contacted with a cell that contains or expresses the polypeptide but the test compound may have no direct contact with the polypeptide. In stead, the test compound may act to induce production and/or activity of a different compound, such as an intracellular second messenger that serves to contact the polypeptide and modulate or change the biological activity of this polypeptide.

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In accordance with the foregoing, the method of the present invention includes cancer modulating agents that are themselves either polypeptides, or small chemical entities, that affect the cancerous process, including initiation, suppression for facilitation of tumor growth, either *in vivo* or *ex vivo*. Such agents may also be antibodies that react with one or more polypeptides encoded by genes present in the amplicons of the invention.

In keeping with the disclosure herein, the present invention also relates to a method for treating cancer comprising contacting a cancerous cell with an agent having activity against an expression product encoded by a gene mapping within regions of chromosomal interest.

The method of the present invention includes embodiments of the above-recited method wherein said cancer cell is contacted *in vivo* as well as *ex vivo*, preferably wherein said agent comprises a portion, or is part of an overall molecular structure, having affinity for said expression product. In one such embodiment, said portion having affinity for said expression product is an antibody.

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In one embodiment of the present invention, a chemical agent, such as a protein or other polypeptide, is joined to an agent, such as an antibody, having affinity for an expression product of a cancerous cell, such as a polypeptide or protein encoded by a gene related to the cancerous process, especially a gene mapping to an amplicon as disclosed herein In a specific embodiment, said expression product acts as a therapeutic target for the affinity portion of said anticancer agent and where, after binding of the affinity portion of such agent to the expression product, the anti-cancer portion of said agent acts against said expression product so as to neutralize its effects in initiating, facilitating or promoting tumor formation and/or growth. In a separate embodiment of the present invention, binding of the agent to said expression product may, without more, have the effect of deterring cancer

promotion, facilitation or growth, especially where the presence of said expression product is related, either intimately or only in an ancillary manner, to the development and growth of a tumor. Thus, where the presence of said expression product is essential to tumor initiation and/or growth, binding of said agent to said expression product will have the effect of negating said tumor promoting activity. In one such embodiment, said agent is an apoptosis-inducing agent that induces cell suicide, thereby killing the cancer cell and halting tumor growth.

Many cancers contain chromosomal rearrangements, which typically represent translocations, amplifications, or deletions of specific regions of genomic DNA. A recurrent chromosomal rearrangement that is associated with a specific stage and type of cancer always affects a gene (or possibly genes) that play a direct and critical role in the initiation or progression of the disease. Many of the known oncogenes or tumor suppressor genes that play direct roles in cancer have either been initially identified based upon their positional cloning from a recurrent chromosomal rearrangement or have been demonstrated to fall within a rearrangement subsequent to their cloning by other methods. In all cases, such genes display amplification at both the level of DNA copy number and at the level of transcriptional expression at the mRNA level.

In accordance with the present invention, said functionally related genes are genes modulating the same metabolic pathway or said genes are genes encoding functionally related polypeptides. In one such embodiment, said genes are genes whose expression is modulated by the same transcriptional activator or enhancer sequence, especially where said transcriptional activator or enhancer increases, or otherwise modulates, the activity of a gene mapping to one of the amplicons of the invention.

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The present invention also relates to a process that comprises a method for producing a product, such as test data, comprising identifying an

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agent according to one of the disclosed methods for identifying such an agent (i.e., the therapeutic agents identified according to the assay procedures disclosed herein) wherein said product is the data collected with respect to said agent as a result of said identification process, or assay, and wherein said data is sufficient to convey the chemical character and/or structure and/or properties of said agent. For example, the present invention specifically contemplates a situation whereby a user of an assay of the invention may use the assay to screen for compounds having the desired enzyme modulating activity and, having identified the compound, then conveys that information (i.e., information as to structure, dosage, etc) to another user who then utilizes the information to reproduce the agent and administer it for therapeutic or research purposes according to the invention. For example, the user of the assay (user 1) may screen a number of test compounds without knowing the structure or identity of the compounds (such as where a number of code numbers are used the first user is simply given samples labeled with said code numbers) and, after performing the screening process, using one or more assay processes of the present invention, then imparts to a second user (user 2), verbally or in writing or some equivalent fashion, sufficient information to identify the compounds having a particular modulating activity (for example, the code number with the corresponding results). This transmission of information from user 1 to user 2 is specifically contemplated by the present invention.

In accordance with the foregoing, the present invention relates to a method for producing test data with respect to the anti-neoplastic activity of a compound, such as a test compound as defined herein, comprising:

- (a) identifying a test compound as having anti-neoplastic activity using a method of the invention, such as measuring the biological activity of a polypeptide encoded by a gene of Table 3 (SEQ ID NO: 1-3049), and
- (b) producing test data with respect to the anti-neoplastic activity of said test compound sufficient to identify the chemical structure of said test compound.

In another embodiment, the present invention provides a method for monitoring the progress of a cancer treatment, such as where the methods of the invention permit a determination that a given course of cancer therapy is or is not proving effective because of an increased or decreased expression of a gene, or genes, mapping to an amplicon as disclosed herein. For example, where there is an increased copy number of one or more of said genes monitoring of such genes can predict success or failure of a course of therapy, such as chemotherapy, or predict the likelihood of a relapse based on elevated activity or expression of one or more of these genes following such course of therapy.

In accordance with the foregoing, the present invention contemplates a method for determining the progress of a treatment for cancer in a patient afflicted with cancer, following commencement of a cancer treatment on said patient, comprising determining in said patient a change in expression of one or more genes, preferably more than one, corresponding to a gene of Table 3 or encoding a polypeptide or transcript of such a gene, or genes compared to expression of said one or more determined genes prior to commencement of said cancer treatment, wherein a change in expression, especially a decrease in expression, indicates positive effects of such treatment, thereby determining the progress of said treatment.

In a preferred embodiment, the detected change in expression is a decrease in expression. In another preferred embodiment, the cancer treatment is treatment with a chemotherapeutic agent, especially an agent that modulates, preferably decreases, expression of a gene identified herein, such as where said agent was first identified as having anti-neoplastic activity using a method of the invention. Thus, in accordance with this aspect of the present invention, a patient, or even a research animal, such as a mouse, rat, rabbit or primate, afflicted with cancer, including a cancer induced for research purposes, is introduced to a cancer treatment regimen, such as

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administration of an anti-cancer agent, including one first identified as having anti-neoplastic activity by one or more of the screening methods disclosed herein. The progress and success or failure of such treatment is subsequently ascertained by determining the subsequent expression of one or more, preferably at least 3, or 5, or 10, of genes mapping to one or more of the amplicons disclosed herein, preferably to the same amplicon, or that encodes a transcript or polypeptide of such a gene following said treatment. In a preferred embodiment, a treatment that reduces said expression is deemed advantageous and may then be the basis for continuing said treatment. The methods of the invention thereby provide a means of continually monitoring the success of the treatment and evaluating both the need, and desirability, of continuing said treatment. In addition, more than one said treatment may be administered simultaneously without diminishing the value of the methods of the invention in determining the overall success of such combined treatment. Thus, more than one said anti-neoplastic agent may be administered to the same patient and overall effectiveness ascertained by the recited methods.

In accordance with the foregoing, the present invention also contemplates a method for determining the likelihood of survival of a patient afflicted with cancer, following commencement of a cancer treatment on said patient, comprising determining in said patient a change in expression of one or more genes, preferably more than one, corresponding to a gene of Table 3 or encoding a polypeptide or transcript of such a gene, or genes, compared to expression of said one or more determined genes prior to commencement of said cancer treatment, wherein a change in expression, es pecially a decrease in expression, indicates positive and life-extending effects of such treatment, thereby determining the likelihood of survival of said treatment.

In a preferred embodiment, the detected change in expression is a decrease in expression and said determined gene, or genes, may include 2, 3, 5, 10 or more of the genes described herein. Thus, the methods of the invention may be utilized as a means for compiling cancer survival statistics

following one or more, possibly combined, treatments for cancer as in keeping with the other methods disclosed herein.

The genes of the amplicons, or regions of interest, identified herein also offer themselves as pharmacodynamic markers (or as pharmacogenetic and/or surrogate markers), such as for patient profiling prior to clinical trials and/or targeted therapies, including combination treatments, resulting from the identification of these genes as valid gene targets for chemotherapy based on the screening procedures of the invention. In one embodiment thereof, the likelihood of success of a cancer treatment with a selected chemotherapeutic agent may be based on the fact that such agent has been determined to have expression modulating activity with one or more genes identified herein, especially where said genes have been identified as showing elevated expression levels in samples from a prospective patient afflicted with cancer. Methods described elsewhere herein for determining cancerous status of a cell may find ready use in such evaluations.

It should be cautioned that, in carrying out the procedures of the present invention as disclosed herein, any reference to particular buffers, media, reagents, cells, culture conditions and the like are not intended to be limiting, but are to be read so as to include all related materials that one of ordinary skill in the art would recognize as being of interest or value in the particular context in which that discussion is presented. For example, it is often possible to substitute one buffer system or culture medium for another and still achieve similar, if not identical, results. Those of skill in the art will have sufficient knowledge of such systems and methodologies so as to be able, without undue experimentation, to make such substitutions as will optimally serve their purposes in using the methods and procedures disclosed herein.

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The present invention will now be further described by way of the following non-limiting example. In applying the disclosure of the example, it

should be kept clearly in mind that other and different embodiments of the methods disclosed according to the present invention will no doubt suggest themselves to those of skill in the relevant art.

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EXAMPLE

Cancerous cells that over-express one or more genes mapping to the amplicons disclosed herein, are grown to a density of 10⁵ cells/cm² in Leibovitz's L-15 medium supplemented with 2 mM L-glutamine (90%) and 10% fetal bovine serum. The cells are collected after treatment with 0.25% trypsin, 0.02% EDTA at 37°C for 2 to 5 minutes. The trypsinized cells are then diluted with 30 ml growth medium and plated at a density of 50,000 cells per well in a 96 well plate (200 µl/well). The following day, cells are treated with either compound buffer alone, or compound buffer containing a chemical agent to be tested, for 24 hours. The media is then removed, the cells lysed and the RNA recovered using the RNAeasy reagents and protocol obtained from Qiagen. RNA is quantitated and 10 ng of sample in 1 μ l are added to 24 μl of Taqman reaction mix containing 1X PCR buffer, RNAsin, reverse transcriptase, nucleoside triphosphates, amplitaq gold, tween 20, glycerol, bovine serum albumin (BSA) and specific PCR primers and probes for a reference gene (18S RNA) and a test gene (Gene X). Reverse transcription is then carried out at 48°C for 30 minutes. The sample is then applied to a Perlin Elmer 7700 sequence detector and heat denatured for 10 minutes at 95°C. Amplification is performed through 40 cycles using 15 seconds annealing at 60°C followed by a 60 second extension at 72°C and 30 second denaturation at 95°C. Data files are then captured and the data analyzed with the appropriate baseline windows and thresholds.

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The quantitative difference between the target and reference genes is then calculated and a relative expression value determined for all of the samples used. This procedure is then repeated for each of the target genes in

a given signature, or characteristic, set and the relative expression ratios for each pair of genes is determined (i.e., a ratio of expression is determined for each target gene versus each of the other genes for which expression is measured, where each gene's absolute expression is determined relative to the reference gene for each compound, or chemical agent, to be screened). The samples are then scored and ranked according to the degree of alteration of the expression profile in the treated samples relative to the control. The overall expression of the set of genes relative to the controls, as modulated by one chemical agent relative to another, is also ascertained. Chemical agents having the most effect on a given gene, or set of genes, are considered the most anti-neoplastic.

SEQUENCE LISTING ON CD-ROM ONLY

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The sequences disclosed herein as SEQ ID NO: 1-3049 in the sequence listing are contained on compact disc (CD-ROM) only (denoted as Filename: Avalon 237 (5,279 kB), 4 copies of which appear on discs denoted Copy 1, Copy 2, Copy 3 and CRF, and which discs were generated on 7 March 2005), which accompanies this application and the contents of said CD-ROMs are hereby incorporated by reference in their entirety. These sequence numbers correspond to cDNA sequences derived from the genes identified in Table 3.

Table 3 - / Amplicon	Table 3 – Amplicon Identification Amplicon Transcript Id	Name	Chromosome	bpstart	pbend
1 _A	FNST00000303924	HAS2	∞	258293	259816
7.7. 7.7.	00000	ىد	ω	258593	2
7.7	0000004666		&	260852	261006
177			ω	6405	62333
ZZZ ZZZ	0328524		∞	373811	373895
Z Z	0000004		æ	375017	392021
7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.	0000314393	NM 014943	∞	375057	394333
7.7. D.1	000	l	ω	2378972	379035
7.7±	000004711		∞	392188	394333
7.1. D.1	0000047		Ø	2398393	398813
7.T.	000004711		æ	2398393	2401120
7.7. 7.0.	00000		∞	2398393	2401120
77	00259512	NM 024295	œ	2398403	2401108
777	0000000	1	ω	2398404	2399032
7 4	0000004711		8	2398768	2399954
7.7 7.7	00000		ω	2399151	2401120
T K	77,500000		8	2404156	2406247
7. K	002828382	NM 145647	æ	2404159	2412076
7.T	00000		ω	\sim	2406621
14.	00309336	O8TAK7	∞	2404606	2409803
17. K	708000	O8TAK7	∞	2406248	2407302
7 K		1	8	2407418	2408
14 1 K	0000006561		∞	124094878	2409801
7 K	0000006562		&	2409902	2412098
17 K	0000008880		∞	2410958	2412098
Al			α	24109	2412098
Al	ENSESTITOUOUUOSOSZ)		

A1	ENST00000318462	Q86UY5	&	124147875 1241777
Al	1006562		ω (151533 12416290
Al	ENSESTT00000065623			124151533 1241/18
Al	ENST00000276699	NM_032899	ω	4151685 124176255
A1	ENSESTT00000065671		ω	24188795 124210200
A1	ENST00000276704	NM 032847	∞	24188931 12421017
Al	9000	Ì	∞	24189023 12421013
A1	006567		∞	4195324 12421013
A1	ENSESTT00000065668		∞	24218685 12423612
A1	3785	ZHX1	∞	24222153 12422477
A1	ENSESTT00000065670		∞	24224524 12424308
A1	9000		∞	24224572 12424310
A1	ENST00000309019		∞	24284858 12428523
A1	3739	NM 014109	∞	24289962 12436518
A1	ENSESTT00000065666	Ì	∞	24294833 12431505
A1	0006566		ω	24305201 12431389
A1	9000		Φ	24315497 12432845
Al	2977		∞	24369449 12437049
AT	_	M 018024	∞	24385553 12441084
Z Z		ľ	∞	24385553 12441084
A1	000656		∞	385601 124410
Al	0006562		æ	24385602 12441084
A1	9000		∞	24385602 12441084
Z Z	8739	FBX032	ω	24471947 12451003
11 1	000		∞	124472004 124500973
Z Z	0006566		∞	124472004 124510034
Z Z Z	00006566		∞	1003
A1	325995		∞	124614600 124621754
Z Z	33005		∞	124614651 124621727
Al	3295		ω	124614654 124621727
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124649681 12465776	124650068 124681	124662584	8 124667216 1247062	8 124737531 1247440		12474930	-	124777101 12477	124934987 124955	124982464 124984	12500483	125014902 1	125045027 12508	125120753 125121	125280819 12534	125282330 125296	125419757 125421	125441637 12	125443596 125	125443	9 12	12545733	8 125457337 1255078	8 125457337 1255079	12545733	12545733	125457339 125472	8 125457339 125507	
	ANXA13			Q8N6F3	NM 144963	Lţ				NM 173684	l	NM 18252	l		Q8WVK5		NM 01795	l		RNF139								•	
ENSESTT0000065661	262219	90000	0006566	334705	LO	ENSESTT00000065657	S	556	ENST00000297628	ENST00000321393	ENSESTT00000049471			\sim	\sim	ENSESTT00000049470	ENST00000328599	ENSESTT0000049469	マ	マ	ENSESTT00000049468	ENSESTT00000049466	ENSESTT00000049464	4946	4946	4945	4946	494)
A	Al	A1	Al	A1	A1	A1	Al	A1	A1	A1	A1	A1	A1 .	A1	A1	A1	Al	Al	A1	A1	A1	A1	A1	7. A	Z Z Z	Z Z Z	7.7.Z	717 	₹ ₹

125472748 125507878 125472748 125507913 125473099 125507913 125507913 125507913 125507947 125518808 125507947 125518807 125519619 125507947 125518807 125521907 125524630 125525191 125526532 125537360 125526532 125537360 125526532 125537360 1255268151 125697188 125942128 125948216 12594452 125991054 125993091 126001545 125993091 126001545 125993091 1260012931 126001094 126012931 126001094 126013531 126001094 126013531 126006063 126013531 126012074 126013531 126012074 126013317 126032404 126013317 126032404
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NDUEB9 MTSS1 SQLE SQLE
ENSESTTOOOOO049465 ENSESTTOOOOO049460 ENSESTTOOOOOO49460 ENSESTTOOOOOO49446 ENSESTTOOOOOO49457 ENSESTTOOOOO049457 ENSESTTOOOOO049453 ENSESTTOOOOO049453 ENSESTTOOOOO049454 ENSESTTOOOOO049454 ENSESTTOOOOO049451 ENSESTTOOOOO049451 ENSESTTOOOOO049450 ENSESTTOOOOO049449 ENSESTTOOOOO049449 ENSESTTOOOOO049449 ENSESTTOOOOO052949 ENSESTTOOOOO052949 ENSESTTOOOOO52949 ENSESTTOOOOO052949 ENSESTTOOOOO052949 ENSESTTOOOOO052949 ENSESTTOOOOO052949 ENSESTTOOOOO052949 ENSESTTOOOOOO52949 ENSESTTOOOOOO52949 ENSESTTOOOOOO52949 ENSESTTOOOOOO52949 ENSESTTOOOOOO52949 ENSESTTOOOOOO52949 ENSESTTOOOOOO52946 ENSESTTOOOOOO52946
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A2 A2 A2 A2	A2 A2 A2	A2 A2 A2 A2 A2	A2 A2 A2 A2 A2	A2 A2 A2 A2 A2 A2

TABLE 3 (Continued)

96825	9692645	9692645	9688724	9692908	9696113	9698024	9699149	9710290	9707682	9707682	9707675	9718204	9732824	9714751	9715073	9743660	9717971	9717962	9719793	9720372	971820	9717975	972062	972003	9718488	972107	972133	972138(
6812 8251	85528	85528	388685	92749	96054	397993	399106	703405	3497	8/0/0/	707171	114374	114374	114424	714424	714736	715054	715793	71595	71604	71605.	71605.	71816	71820	71823	71962	72061	72104
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STK24-004	00-		OAAM8Õ	bA295B17.5-001	bA295B17.2-001	bA295B17.3-001	bA295B17.4-001	SLC15A1-001	SLC15A1	SLC15A1-002	014496	bA155N3.2-010	bA155N3.2-001			DOC9 HUMAN	bA155N3.2-013	bA155N3.2-012	bA155N3.2-009			bA155N3.2-011	3.2-00	55N3.	55N3.3-00	5N3.		bA155N3.2-008
ENSESTT00000040364	1300286	0004036	ENST00000313290	OTTHUMT00013002856	0130028	013002	013002	01300	21855	01300	ENST00000313260	0130	001300	00000	0404	ENST00000301980	000130	300	300289	000404	0004	OTTHUMT00013002900	1300289	001300289	01300288	00130028	000004049	30028
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97210 72176 72340	839 325 325	727230	730001	730569	730574	752384	754083	754102	754669	754669	754765	755102	755102	97551031	755108	755108	755110	755114	755114	755116	755116	755117	755117	755166
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OTTHUMT00013002963 OTTHUMT00013002962 ENST0000245361 OTTHUMT00013002964 ENSESTT0000040467 ENSESTT00000040466	0004046 0004046 0004046 1300296 0004047	ENSESTT00000040469 ENSESTT00000040473 ENSESTT00000040472 ENSESTT00000040474 ENSESTT00000040474	OTTHUMT00013002970 OTTHUMT00013002972 ENSESTT0000040477 OTTHUMT00013002980	ENSTO0000323941 OTTHUMT00013002981 OTTHUMT00013002974 OTTHUMT00013002976 ENSESTT00000040339 ENSESTT00000040339
A2 A2 A2 A2 A2	A2 A2 A2 A2	A2 A2 A2 A2 A2	A2 A2 A2 A2	A2 A2 A2 A2 A2 A2

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98124280 98209116 98209116 98213298 98215060 98215103 98216572 98216572 98216572 98216572 98216572 98332294 98332294 98332294 98332599 98334544 98334944	83350 83350 83351 83357 84357 84393 84393 84393 84393 84393
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OTTHUMT00013002978 OTTHUMT00013002984 ENSESTT0000040310 ENSESTT0000040311 ENSESTT0000040312 OTTHUMT00013002986 ENSESTT0000040313 OTTHUMT00013002985 ENSESTT0000040314 OTTHUMT00013002994 ENSESTT00000245295 ENSESTT0000040315 OTTHUMT00013002995 ENSESTT0000040316 OTTHUMT00013002997 ENSESTT0000040317	013002 000040 0013002 013003 013003 013003 013003 0013003
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TABLE 3 (Continued)

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ENSESTT0000040324 ENST0000310787 OTTHUMT00013003017 OTTHUMT00013003010 ENSESTT00000040325	OTTHUMT00013003014 ENSESTT0000040326 ENSESTT0000040327 ENSESTT00000040328	01300301 00004032 01300301	300	ENSESTT00000040330 OTTHUMT00013003018 OTTHUMT00013003052 ENST00000257302 ENSESTT00000040335 ENSESTT00000040336	4033 0305 0305 4033	OTTHUMT00013003056 OTTHUMT00013003053 OTTHUMT00013003034 OTTHUMT00013003026
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Q8TBX6	Q8NDZ2 Q8IZ15 NM 020444	NM_173664 CGB7_HUMAN NM_138820	CLTB NM_001834 NM_014613
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C17	ENSESTT000000551		S	5994575 17600069
Z Z	ENSESTT00000026252		2	5994607 17600069
A3	ENST0000303991	NM 052899	2	6003728 17601
A3	ENST0000335532	Q96PZ4	5	6004664 17600776
A3	ENST00000310112	SNCB	72	6028134 17603789
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A3	FNSFSTT00000025931		ιΩ	6052504 17605406
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176897716 17703820 76898295 17690431 76909731 17691609 76911807 17691767	76919402 1769246 76926890 1769437 76926890 1769616 76945068 1770940	76999291 17700262 76999295 17713328 76999295 17713609	99300 1770 99308 1771 00737 1770 00783 1771	77001245 17713671 77007252 17715069 77023996 17703819	77024173 17703819 77024246 17703711 77024246 17703711	77031099 17703711 77031469 17703819 77031684 17703720	77031702 17703711 77042509 17704886 77044585 17705045 77045241 17705044 77045345 17705098
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ENSESTT0000026016 ENST00000330641 ENST00000331981 ENST00000312943 ENST00000274826	ENST00000330503 ENSESTT00000026010 ENST00000329540 ENSESTT00000026015	ENSESTT00000026011 ENSESTT00000026013 ENSESTT00000026012	ENST00000328179 ENSESTT00000026014 ENSESTT00000035756	ENSESTT00000035758 ENSESTT00000035760 ENSESTT00000035760	ENSTOUCOUS33469 ENSESTT0000035801 ENST0000292374 ENST0000331561	ENST00000331867 ENSESTT00000035800 ENSESTT00000035802)3323)3317)3333)0000
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DDX41	NM_019057	NM_017510	D4GALL / Q9HAI8	NM_173663		Q8TE30	THOC3	Q9H7L9 PROP1		Y341_HUMAN YE01_HUMAN
ENSESTT0000035799 ENST0000330228 ENSESTT0000035796	00274788 0000003579 0000003579	TT0000003 000033259	94L 003 285	03181 03031	0000032461 STT00000003	ENST00000329355 ENST00000331417	0030315 0030315 0000003	32215 08304	SESTT00000003 SESTT00000003 SESTT00000003	ENSTOUDUS32649 ENST00000274605 ENSESTT0000035767 ENST0000313376
A3 A3 A3	A3 A3 A3	A3 A3	A3 A3	A3 A3	A3 A3	A3 A3	A3 A3	A3 A3	A3 A3	A3 A3 A3

177671744 177688239 177671744 177689170 177684377 177689170 177690065 177694497 1777690069 177694497 177745132 177727901 177745132 177751397 177745132 177751397 177745132 177751397 177745132 177751563 177745132 177751762 177745132 177751762 177745132 177751762 177745132 177751762 177745132 177751762 177745132 177751762 177745132 177751762 177745132 177751762 177745132 177751762 177745132 177751762 177749103 177751762 177749103 17777119 177749189 177763185 177749189 17776179 177749189 17772179	77891469 17789285
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8143870 178154 144219 1781713 153016 1781594 157479 178167 157835 178167 158920 178171 159118 178167 160838 178167	78252662 17826962 78267657 17826994 78307485 17830912 78307800 17832294 78400555 17842336	78400555 1784256 78401325 1784069 78472120 17847330 78481825 1785070 78483299 1785053	78505697 1785330. 78509517 1785307. 78522259 1785355. 7853580 1785368 78564407 1785735	8601202 1786212 8623365 1786240 8653824 1786541 8654498 1786653 8661813 1786633
ម្យាល មា មា មា មា	ប្រហ្វាហ	ម្នា ម្នា	ប្រហ្វា	ប្រសាល្យ
CLK4	ZNF354A	ZNF354B ZNF271 ZNF454	Q8NHA9 GRM6	ZNF354C ADAMTS2
ENSESTTO000025813 ENST00000316308 ENSESTT0000025818 ENSESTT0000025816 ENSESTT0000025814 ENSESTT0000025814 ENSESTT0000025814	ENSESTIO000306591 ENSESTT0000025812 ENSESTT0000025811 ENST00000331699	ENSESTIO000322434 ENST00000322434 ENST00000320451 ENST00000320129 ENST00000320129	ENST0000319065 ENSESTT0000025802 ENST0000231188 ENSESTT0000025810 ENSESTT0000025803	ENST0000315475 ENSESTT00000025809 ENSESTT00000025806 ENSESTT00000025807 ENSESTT00000025807

78691731 17869 3692740 178699 3692740 178699 3917905 178915 39043326 179129 3909034 179129 3909034 179129 3100164 17914 3100278 17914 3100278 17914 3133252 17914 3140510 17914 3150871 17915 3150871 17916 3150871 17916 3150871 17916 315147 17916 3151282 17916 3151282 17916 3151282 17916	79152814 1791577(79154867 179159897) 79154867 1791603679157887 1791603679184188 1791868686867 79184188 1791868679184188 1791876496868
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ADAMTS2 NM_030970 HNRPH1	Q8NA96 Q86VE1
ENSTOOOOO274609 ENSESTTOOOOOO25805 ENSESTTOOOOOO25804 ENSESTTOOOOOO35851 ENSESTTOOOOOO35852 ENSESTTOOOOOO35854 ENSESTTOOOOOO35855 ENSESTTOOOOO035855 ENSESTTOOOOO035857 ENSESTTOOOOO035857 ENSESTTOOOOO035857 ENSTOOOOO35857 ENSESTTOOOOO035916 ENSESTTOOOOO035916 ENSESTTOOOOO035918 ENSESTTOOOOO35918 ENSESTTOOOOO035918 ENSESTTOOOOO35918 ENSESTTOOOOO35918 ENSESTTOOOOO35910 ENSESTTOOOOO35910 ENSESTTOOOOO35910 ENSESTTOOOOO35910	3.2 3.591 3.591 3.585 3.585 3.585
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79215692 1792176 9230857 17923135 9235589 17924504 9235589 17926755 9240421 17926755 9246533 17926755	79269772 17931394 79303154 17930785 79330648 17933317 79330696 17933317 79332229 17933317 79332243 17933317	9334262 179343 9334633 179338 9334633 179338 9334633 179338 9334883 179338 9334883 179343 9334883 179343 9335007 179343
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CANX	MAML1 NM_024978 LTC4S	MGAT4B
ENSESTT0000035907 ENST00000329156 ENSESTT0000035861 ENSESTT0000035865 ENSESTT00000035865 ENSESTT00000035865 ENSESTT00000035863	ENST00000292599 ENSESTT0000035866 ENST00000298607 ENST00000292596 ENSESTT00000035869 ENSESTT00000035870 ENSESTT00000035870	ENSESTTO000035906 ENSESTT00000035906 ENSESTT00000035902 ENSESTT00000035895 ENSESTT00000035896 ENSESTT00000035896 ENSESTT00000035897 ENSESTT00000035897 ENSESTT00000035897 ENSESTT00000035897 ENSESTT00000035899
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1621 1797966 186 17982853 361 17987526 391 17986831 517 17986748 152 17988998 531 17988998	80065924 18011086 80065968 18008726 80065968 18010118 80112873 18011315	30126767 18012814 30126768 18012814 30139821 18014808	30145626 18018620 30162667 18016664 30166890 18018628	30229572 18023042 30275785 18027672 30327203 18032862 80327203 18032876 80327210 18035220	0327543 180339 0328296 180329 0329112 180335 0329332 180345 0332068 180352 0332092 180339 0332309 180345
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GEPT2	NM_015455	SCGB3A1	FLT4	Q8NHB0 Q8NGV0 MGAT1	Q8NBL8
ENST 00000328081 ENSEST 0000035876 ENSEST 0000035874 ENSEST 0000035875 ENSEST 0000035875	54	ENSTOUDUSS2929 ENSESTT00000035680 ENST00000292641 ENSESTT0000035679	57	ENST00000315712 ENST00000307832 ENSESTT00000035676 ENSESTT00000035675	ENSESTT0000035663 ENST00000307826 ENSESTT00000035662 ENSESTT00000035661 ENSESTT00000035665 ENSESTT00000035664 ENSESTT00000035664
A3 A3 A3	A3 A3 A3	A3 A3	A3 A3	A3 A3 A3 A3	A3 A3 A3 A3 A3 A3

180344545 1803467 80345508 18035220 80345511 18034679 80384273 18039722 80384335 18039794	59 18038776 17 18038813 77 18039721	80435821 18048756 80435955 18044819 80448211 18048756	30525529 18054302 30582152 18059022 80589782 18059196	80590141 18059818 80592305 18059597 80635802 18063737 80650805 18065192	0691605 18069259 0728586 18073109 0731275 1807368 0734864 1807397 0739916 18074178	159 899 917 651 071
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	NM_152283	NM_024850	BTNL3 NM_152547	Q8N324	Q8NGV1 - - - -	TRIM7 Q96Q10 TRIM41 GNB2L1
ENSESTT00000035658 ENSESTT00000035657 ENSESTT00000035673	ENST0000330037 ENST00000302108 ENST00000302108	ENST0000231229 ENSESTT0000035641 ENSESTT0000035642	ENST00000301996 ENST00000298708 ENSESTT00000035643	ENST00000327705 ENSESTT0000035644 ENST00000328095 ENST00000328767	ENST00000329365 ENST00000328275 ENSESTT0000035645 ENST00000274773 ENSESTT0000035646	ENST00000334421 ENST00000312487 ENST00000315073 ENSESTT00000035647 ENSESTT00000035648
						A3 A3 A3 A3

80773591 1807762 30783187 18078385 30791085 18079685 30792443 18079288 30793051 18079692 30793672 18079698	30794077 1807974 30797875 1808009 30797875 1808009 30797875 1808647 30854088 1808647 30866068 1808869	30903950 18090488 30988607 18099166 30990904 18099162 31008629 18100908	2489 26867 5304 26867 0528 26762 9569 26762 6741 26762 9173 26810 2654 26839 2654 26810 2654 26839 2654 26839	6839038 2686724 6970970 2697218 7031241 2705105 7031241 2705106 7031241 2705106
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NM_022907	TRIM52	O4F3_HUMAN	FLT1-001 FLT1	bA57H24.1-001 C13orf12 bA97E23.1-001 bA97E23.1-002
00300		3864)003565)003565 32522	01300070 282397 000003741 000003742 000003741	
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70510 703499 705047 705033	709073 709110 708298	708527 709111 709615 709527	715107 787554 787589 762269	27622691 27622691 27673230 27680052 27875873	786944 785988 785988 785988	7.96772 7.90832 789164 789454
70312 703127 703287 704448	707285 707285 707338	707340 708547 709452 709484	715069 739745 739745 761151	11480	780092 784868 784903 784903	788154 78866 78890(78945)
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bA97E23.2-002	78	bA97E23.3-001	bA161P17.1-001 Q8N5E2 bA274A8.1-002 bA351N4.3-003		Q8N642 bA274A8.2-001	SLC7A1-001 SLC7A1 SLC7A1-002
ENSESTT00000037329 ENSESTT0000037330 ENSESTT0000037342 ENSESTT0001300715	0026694 000130(000000	ENSESTT00000037340 ENSESTT00000037339 OTTHUMT00013000718 ENSESTT00000037338	01300072 255289 01300073	TTHUMT0001300 TTHUMT0001300 NSESTT0000003 TTHUMT0001300	ENSESTT0000037332 ENST0000323380 OTTHUMT00013000730 ENSESTT0000037337	OTTHUMT00013000732 ENST00000266949 OTTHUMT00013000733 ENSESTT00000037335
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TABLE 3 (Continued)

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	96486	01406	01795	13650	13654	13891	313913	313975	323809	329078	331004	331004	331004	34797	35262(35801	85804(85806	862758	862758	86276	86276	86682	86682	86884	87134	87134
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ST.C7A1-003	69IN8Ö	Q8TE30	Q9P1E1	UBL3-001					DA90M5.2-001	DA90M5.4-001		Q9H523	DA90M5.1-001	DA629E24.1-001		bA374E3.1-001		NM 032116	ł				bA374E3.2-001	ı	bA374F3.3-001	ω.	
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TABLE 3 (Continued)

5 291365 2913656 2911653 2918278 2918302 2925553	2925553 2925553 2929770 2929770	2929658 2929796 2930362 2930361 2930472	2930 2930 2937 2937 2937 2937 0 2937 0 2937 0 2957 0 2957 0 2957 0 2957 0 2957 0 2957	29520
91076 10766 11447 17534 17534	25468) 25469 27832 27832	328953 330280 330281 330363	L 8 8 8 0 4 7 7 L L L L L L	95087
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ALOX5AP-001 ALOX5AP-002 bA469L23.2-001	bA252M21.1-001 NM_032849 bA252M21.2-001	• •	- 4-7-7-7-7-7-7-7-7-7-7-7-7-7-7-7-7-7-7-	
OTTHUMT00013000806 ENST0000255317 OTTHUMT00013000807 OTTHUMT00013000804 ENSESTT0000042392	300081 004239 8987	130 130 000 000 000 130	300081 300082 300082 300082 300082 1300083 1300082 1300083 000424 000424 000424	ENSESTT00000042403
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			P16.2-00 P16.2-00	73P1 73P1		1				HSPH1 HSPH1		
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29520623 29523880 29522321 29522321 29522321 29520230 29520230 29520230 29520230 29522321 29523880 29523880 29523880 29523880 29523880 29523880 2952321 2952321 2952321 2952321 2952321	97044(96568)	96568 96763 96850 01750 03255
29510418 29510418 29510418 29510574 29510574 29510574 29510913 29510913 29510913 29510913 29510913 29510913 29510913 29510913 29510913 29510913 29510913 29515928 29515928 29515928 29515928 29515928 29515928 29515928	957211	963254 967539 968342 01116 02189
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752263	522636	522677	26	516474		75227888	5225	52252	522636	226	522677	522788	52267	523604	75236046	523604	5236	523604	523604	525529	528934	528934	528939	528939	28939	29568	52424	4681
51565	515653	515653	75156536	516452		17680	953	5195	51953	519538	5195	51954	5223	2839		522912	522918	22933	522937		523774	S	75237744	75237744	52	75237744	3774	75237749
7	7	7	7	7		7	7	7	7	7	7	7	7	7	_	7	7	7	7	7 .	7	7	7	7	7	7		7
				Hs_7_c1165	mbhmh h 73557902	339488			•			POR		TIAMI														
ENSESTT00000040190	ENSESTT00000040191	0000402	000004020	00700741	OTTHUMT00007006487		FNSFSTT00000040200	TT00000401	00004019	000004019	00004019	65302	000004	00700	0000040	0004025	000040	00004025	00004025	00004024	0000402	00004024	0004023	0004023	0004024	000040	00004025	000040
A7	A7	A7	A7	A7	A7		A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	Z Z Z	A7	A7	A7	A7	Å7

0 750550	00/07/01 07/1/07	3//49 /526340	37749 7528934	37749 7528939	37749 7528939	37749 7528941	37749 7529568	37875 7527193	55146 7528937	88063 75288	89457 7530800	89482 7530801	89482 7530802	89536 7530800	05745 7530800	12957 7531320	15857 75	40845 7534281	4984	54317 7535484	54317 753548	90863 7539096	15144 754185	43300 755014	43300 755067	43307 75506	76389 7550145	76473 7552	
Ù	י) כחנ	797	752	752	752	752	752	752	752	752	752	752	752	752	753	753	753	753	753	3	753	753	754	754	754	75	7	7 754	
						MK-STYX		MSTY HUMAN				MDH2	MDH2			Hs 7 c3073	Hs_7_c1171	Hs_7_c5123	Hs_7_c1174		Hs 7 c1175	. Hs_7_c1176	Hs_7_c1177						mbhmh h 73557902 74457901 m
のとことのこのこのできませいはいれば	7000004004	000004024	ENSESTT00000040246	ENSESTT00000040241	ENSESTT00000040242	OTTHUMT00007006727	ENSESTT00000040237	ENST00000248600	ENSESTT00000040243	ENST00000315790	ENSESTT00000040204	ENST00000315758	OTTHUMT00007007151	ENSESTT00000040205	000004020	OTTHUMT00007007750	OTTHUMT00007007439	OTTHUMT00007008045	OTTHUMT00007007443	ENST00000332057	OTTHUMT00007007445	OTTHUMT00007007446	OTTHUMT00007007447	ENSESTT00000040208	ENSESTT00000040207	00000040	ENSESTT00000040210	$C_{\mathbf{V}}$	OTTHUMT00007006504
ا ا	֝֞֞֝֞֝֞֝֞֝֟֝֓֞֝֞֝֟֝֓֓֓֞֝֞֓֓֓֞֝֞֓֓֞֝֟	A /	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7

TABLE 3 (Continued)

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		_	52869	567	554570	554570	60040	0021	560039	560350	62109	565110	563896	563503	568347	568346	568347	568336	572401	572417	572210	572412	572419	574739	574700	57219	571255	71253	75747401
		557.3	552405	554399	554401	554401	556820	55709	557099	60253	563073	63073	563105	563146	566634	566637	567097	567432	70307	570311	570311		570313	57031		570315	71150	7115	75743571
(75527249		7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
(75476474		NM 153043	l	HSPB1	HSPB1	YWHAG	YWHAG			SRCRB4D	SRCRB4D		Q96BF5	ZP3A	ZP3								DTX2	DTX2		Hs 7 c1183		
1	7																												
	896_13	ENSESTTOUOUU040ZLL	6284	ENSESTT00000040213	OTTHUMT00007006552	ENST00000248553	OTTHUMT00007006186	ENST00000307630		ENST00000325070	ENST00000275560	000	ENSESTT00000040234	0297799	0	ENST00000257652	ENSESTT00000040214	ENSESTT00000040215	SESTT0000004021	ENSESTT00000040217	SESTT0000004021	ENSESTT00000040219	ENSESTT00000040220	0	ENST00000324432		OTTHUMT00007007472	ENST00000329896	FNGFGTTONON04022
	[A/.	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	77

75756864 75755467 75756483	75661	575665 575539	575662	577410	577410	78170		578286	78175	578022	579292	586709	586749	586749	586865	586865	75867011	586816	589230	624571	621065	621062	21836	2317	76257202
75751969 75751972 75752017	75205	575205 575216	575294	576333	576592	77291		577409	577537	577757	579102	585139	585139	585139	585139	585157	75852858	585958	589180	620125	620960	620966	621408	22002	76243584
, L			7	7	7	7		7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	UPK3B	UPK3B			Hs_7_c1187		mbhmh_H_DJ1158B01	fgenesh2.2			Hs 7 c1186]			POMZP3	POMZ P3			Hs 7 c1194	Hs_7_c1196	Hs_7_c1197	 			PMS2L11
ENSESTT00000040223 ENSESTT00000040224	334348	ENST00000257632	00004022	ENST00000333674	OTTHUMT00007007476	ENST00000332397	OTTHUMT00007007156		ENSESTT00000040233	ENST00000328339	0	ENSESTT00000040229	ENSESTT00000040228	ENSESTT00000040232	OTTHUMT00007006838	ENST00000310842	ENSESTT00000040230	ENSESTT00000040231	00700	OTTHUMT00007007518	OTTHUMT00007007520	ENST00000331556	0000	3075	ENST00000162863
A7 A7	A7	A7	A7	A7	A7	A7	A7		A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7

65201	653657	652398	76536589	657138	657174	656885			699099	657174	76567945	664747	659675			665327	665723	675176	683927	76881437	684233	688064	684233	688143	688143	688143	689500	88143	688925
64783	650133	650150	76523852	652385	655211	655212			655272	655299	76562091	657160	657164			61143	663836	675139	677886	88	677890	677891	680540	684860	684860	684860	684860	87363	687500
7	7	7	7	7	7	7	3517		7	7	7	7	7	8517		7	7	7	7	7	7	7	7	7	7	7	7	7	7
Q96MS1	Q9P223					Q9Y4L9	mbhmh_nh_h_75248	76148516 m	18931739			Q8ND73		旧	76148516 m	18931739		Q9BXE6		PTPN12		PTPN12							
ENST00000285871	ENST00000257657	ENSESTT00000037262	ENSESTT00000037264	ENSESTT00000037263	ENSESTT00000037284	ENST00000257626	OTTHUMT00007007104			ENSESTT00000037285	ENSESTT00000037286	ENST00000334003	ENSESTT00000037283	OTTHUMT00007007105			ENSESTT00000037282	ENST00000310324	ENSESTT00000037265	0700682	ENSESTT00000037266	ENST00000248594	ENSESTT00000037267	ENSESTT00000037269	ENSESTT00000037270	ENSESTT00000037271	ENSESTT00000037268	ENSESTT00000037272	ENSESTT00000037281
A7	A7	A7	A7	A7	A7	A7	A7			A7	A7	A7	A7	A7			A7	A7	A7	A7	A7	A.7	A7						

17667118 7759186 7759281 7759572 7818779	.7822324 11784845 .7822324 11784905 .7831482 11784910	17842855 11785381 17842859 11785912 17842865 11785290 17842865 11785570	17842866 11807416 17842868 11785576 17861020 11788053	7862486 11787699 7885713 11790518 7917336 11794304 7920750 11792838	17943058 11797049 17962945 11797049 17974982 11797619 18039391 11807418	18742261 1187432 18772051 1188208 18889344 1188903 18889622 1188904	18920227 1190296 18921825 1189346
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GDAP2	Q9H141 WDR3	į	Q8NAZ1			Q9UN81 TBX15	WARS2
ENSESTT0000003522 ENSESTT0000003520 ENSESTT0000003521 ENST00000263166 ENSESTT00000003504	00000309112 00000183319 STT0000000350	0000351 0000351 0000351	86203 00000351 00000351	00000351 00000351 00000351	ENSESTT00000003509 ENSESTT0000003508 ENSESTT0000003506 ENSESTT0000003436	3436 20715 30000	ST00000235521 SESTT0000000034
A8 A8 A8 A8	A8 A8 A8	A A A A A A A A A A A A A A A A A A A	A A A A A A A A A A A A A A A A A A A	A8 A8 A8	A8 A8 A8 A8	A8 A8 A8	A8 A8

18922024 1190296 9015816 11901629 9035413 11903603 9217196 11921981 19257783 11928124 19257783 11928124	19270090 11928284 19304149 11940364 19304154 11931127 19304167 11930860		19396481 11940364 19456897 11946107 19485270 11948587 19494238 11949438 19511709 1195124(19600896 11963327 19600896 11963327
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	HAO2 Q8TDP9	HSD3B2 Q8TDP9 Q9H1N0 Q9H1M9	HSD3B1 Q9UDK8 Q9UD07 Q96IT2
ENSESTTO00003432 ENST0000333224 ENSESTT000003526 ENSESTT0000003527 ENSESTT0000003529 ENSESTT0000003531 ENSESTTO000003531	5945 1050 000353 000353	ST00000333709 ST00000333709 ST00000332017 ST00000256586 ST00000286193 ST00000331024 SESTT000000353	ENSESTT000000353/ ENST00000335580 ENST00000331009 ENST00000271263 ENSTST00000273539 ENSESTT0000003539
A8 A8 A8 A8 A8 A8	A A A A A A A A A A A A A A A A A A A	A A A A A A A A A A A A A A A A A A A	A8 A8 A8 A8 A8

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PHGDH					HMGCS2				Q8NER6			REG4	,	SLC26A8-001	SLC26A8	SLC26A8			MAPK14-002	MAPK14-001	NM 139014	MAPK14	MAPK14		dJ179N16.3-001	MAPK13-005			COO C 1717 414
ENST00000263167	0000000354	ENSESTT00000003541	ENSESTT00000003542	ENSESTT00000003543	ENST00000256633	ENSESTT00000003552	00000035	00000	ENST00000324032	0	ENSESTT00000003550	ENST00000256585	0	00060062	ENST00000229784	←	ENSESTT00000033005	0000	0000600627	900900	NST0000022	22	003	00000	OTTHUMT00006006258	0	0000032	000032	
A8	A8	A8	A8	A8	A8	A8	A8	A8	A8	A8	A8	A8	A8	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A 9	, (

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A9	OTTHUMT0000606266	MAPK13-001	9	361449	861546
<u>ත</u>	ENST00000211287	MAPK13	9	514511	515469
A9	0		9	514514	515469
ച	SESTT00000032		9	514514	515590
A9	ENSESTT00000032941		9	514514	515153
9	00000032		9	514520	515469
19	0000032		9	514520	515590
64	ENSESTT00000032944		9	514527	514603
49	9009000	MAPK13-004	9	514529	515383
49	OTTHUMT0000606267	MAPK13-002	9	514550	515114
949	OTTHUMT00006006280	BRPF3-001	9	521140	524741
49	ENST00000322766	BRPF3	9	521140	524742
A9	00		9	621202	521524
A9	000003294		9	621590	522449
A9	00000	BRPF3-002	9	622513	524741
A9	ENST00000211291	Q9NWM1	9	622598	624535
A9	ENSESTT00000032947		9	622866	623258
A9	00000		9	623991	624614
A9	OTTHUMT00006006284	dJ50J22.1-001	9	628511	631005
A9	ENST00000312917	PNPLA1	. 9	630603	632322
A9	00	dJ50J22.5-001	9	631703	632744
A9	OTTHUMT00006006290	dJ50J22.3-001	, 9	633180	633406
A9	9009000	.2-00	9	638082	640241
A9	OTTHUMT00006006287	dJ50J22.2-002	9	638082	640241
A9	ENST00000229480	ETV7	9	36380827	36402349
A9	ENSESTT00000033001		9	9	640240
A9	OTTHUMT00006006292	dJ50J22.4-001	9	640146	640662
A9	ENST00000316266	NM 152990	9	640518	641516
A9	OTTHUMT00006006296	dJ347L7.1-001	9	641509	645752
A9			9	645739	64583

365051	650577	36499460	36503191	550577	550577	656210	656210	652222	656210	36616435	661754	661806	661	661740	6899	0	669914	6701	670197	670196	670055	670195	99	36695312	36695312	36743433	36745385	36752338	36752618
364573	645761	36484759	36499410	36499410	650151	36508524	650853	36510468	36530077	36608994	36608994	006099	660902	661139	36688401	36688449	9	36692420	36693290	669334	6933	669335	36693358	36693403	36693403	6737	36737257	36751637	36751682
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E69	dJ108K11.3-00					STK38-001	STK38					SFRS3-001	SFRS3-002	SERS3		dJ193M11.1-00	CDKN1A-005		CDKN1A-001	CDKN1A	CDKN1A-002		CDKN1A-004	CDKN1A-003		dJ431A14.3-00		Q8TDV1	dJ431A14.4-00
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ENST00000265344	OTTHUMT00006006298	ENSESTI00000032950	00000329	ENSESTT00000032951	000003295	OTTHUMT00006006300	ENST00000229812	ENSESTT00000032999	ENSESTT00000032996	ENSESTT00000032955	000003295	OTTHUMT00006006302	OTTHUMT00006006303	ENST00000244437	ENST00000317631		OTTHUMT00006012688	00000	OTTHUMT00006012684	024474	OTTHUMT00006012685	ENSESTT00000032957	OTTHUMT00006012687	OTTHUMT00006012686	000003295	0006011		031039	OTTHUMT00006006308
A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A 9	A 9	9 X	D D	A9	A9

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	OTTHUMT00006006311	dJ431A14.5-002	ڡ	6755	57720
	ENST00000244751	CPNE5	9	75541	85400
		dJ431A14.5-001	9	75541	85463
	000329		9	15831	77201
	0	dJ431A14.5-003	9	576001	77201
	0000329		9	27600	
	000		9	576001	578033
	0000329		9	576002	377202
	OTTHUMT00006006351	PPIL1-002	9	586945	587326
	00600635	PPIL1-001	9	586945	388965
		PPIL1	9	58694	388962
	0000		9	587009	388965
	00003298		9	587025	588650
	009000	dJ90K10.2-001	9	588650	593918
	900900	dJ90K10.2-004	9	590048	593113
	9009000	dJ90K10,2-002	9	590049	593815
	000600631	l l	9	590049	593815
	0	C6orf89	9	590049	594117
	0000		9	690054	593861
	0900	dJ90K10.2-005	9	690054	693820
	ENSESTT00000032960		9	690055	692922
	0000032		9	6069	693861
	OTTHUMT00006006326	dJ90K10.3-001	9	694321	694349
	0000063	dJ90K10.4-001	9	69	69593(
	297048	PI16	9	906969	697946
		dJ90K10.5-001	9	06969	69794
	0	•	9	69	697400
	000003296		9	69693	697883
	000003296		9	36969383	∞
	00900	dJ90K10.5-002	9	91169	691929
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36991863 37000929 36992788 37000795	700079	700061	/000/4 698554	699230	698738	700079	698730	704292	702665	702831	704316	704288	706003	705982	710649	710643	718577	7.18577	719005	719005	719005	718887	719005
36982772 36982772 36982772 36983213 36983213	331	698336	69833 69833	698354	698409	698466	698468	702027	702028	702030	702033	704043	705946	705956	710585	710594	718478	718478	718483	718484	718578	37187099	718710
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dJ90K10.6-002 dJ90K10.6-008 dJ90K10.6-001	:	10	MTCH1 6-004 6	dJ90K10.6-003	dJ90K10.6-005		dJ90K10.6-006	EGD2-001			FGD2		dJ405J24.2-001	095101	dJ441G21.1-001				PIM1-003	PIM1		PIM1-004	
OTTHUMT00006006335 OTTHUMT00006006341 OTTHUMT00006006334 ENSESTT00000032965	ENSESTT00000032966	0000600634	ENST00000259958 OTTHUMT0006006337	OTTHUMT00006006336	000000083	96	OTTHUMT00006006339	OTTHUMT00006006356	ENSESTT00000035539	ENSESTT00000035540	ENST00000274963	ENSESTT00000035541	OTTHUMT00006006354	ENST00000297147	OTTHUMT00006006358	03	ENSESTT00000035542	ENSESTT00000035543	000601270	ENST00000259722	0	00006012	
A9 A9 A9 A9	A9	A9	A9 A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9

710007	1 9005	1 6	27278	23366	27226	73386	127278	34760	129420	134760	734760	133928	740936	738620	739599	740587	739164	740586	740587	740587	740587	747423	745871	747423	747669	749613	<u></u>	74	37488203
011011	11011		22681	122681	122706	122982	123326	127240	127249	129896	733132	733181	136868	736871	136875	738350	738352	738355	738355	73835	73915	744784	744785	744785	744785	744785	745026	746	747428
		0 . CUU-LMID	5M6.2-001		6.2-002		9	dJ744I24.2-001 6	9	C6orf197 6		9	RNF8-001 6	9	RNF8 6	9	RNF8-002 6		9	9 .	9	9	dJ153P14.1-009 6			3P14.1-001	015050	1 - 008	9
() () () () ()	12T09000	ENSESTT0000035546	\circ	0316899	00	ENST00000316909	00	09000	ENSESTT00000035547	22949	00	000	9009000	ENSESTT00000035550	29866	ENSESTT00000035551	OTTHUMT0000606367	000035	00003555	00003555	3555	003555	00060063	0003555	0600637	90090	59729	09000	00003555
•		A 6		A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A 9	A 9	6 A	64	O A	21 P	A9

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WHAT IS CLAIMED IS:

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- 1. A method for identifying an antineoplastic agent, comprising:
- (a) contacting a test compound with a cell that expresses one or more amplicons of Table 2 having an amplification ratio of at least 2.0; and
- (b) determining a change in said amplification ratio due to said contacting;

wherein a change in said amplification ratio due to said contacting indicates that said test compound has gene modulating activity

thereby identifying said test compound as a gene modulating agent.

- 2. The method of claim 1 wherein said change in expression is a decrease in expression.
- 3. The method of claim 2 wherein said decrease in expression is a decrease in copy number of the gene.
 - 4. The method of claim 1 wherein said cell was genetically engineered to express said amplicon.

5. A method for identifying an antineoplastic agent, comprising:

- (a) contacting a test compound with a cell that expresses at least one gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 3049 and under conditions promoting expression of said gene; and
- (b) determining a change in expression of said gene as a result of said contacting

wherein a change in expression indicates gene modulation thereby identifying said test compound as a gene modulating agent.

6. The method of claim 5 wherein said change in expression is a decrease in expression.

7. The method of claim 5 wherein said decrease in expression is a decrease in copy number of the gene.

- 8. The method of claim 5 wherein said gene comprises a nucleotide sequence of one of SEQ ID NO: 1 3049.
 - 9. The method of claim 5 wherein said cell was genetically engineered to express said gene.
- 10. A method for detecting the cancerous status of a cell, comprising detecting elevated expression in said cell of at least one gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 3049 whereby such elevated expression is indicative of cancerous status of the cell.

- 11. The method of claim 10 wherein said elevated expression is an elevated copy number of the gene.
- 12. A method for identifying a compound as an anti-neoplastic agent, 20 comprising:
 - (a) contacting a test compound with a polypeptide encoded by a gene selected from SEQ ID NO: 1-3049,
 - (b) determining a change in a biological activity of said polypeptide due to said contacting,
- wherein a change in activity indicates anti-neoplastic activity and thereby identifies such test compound as an agent having antineoplastic activity.
- 13. The method of claim 12 wherein said change in biological activity is a decrease in biological activity.

14. The method of claim 12 wherein said biological activity is an enzyme activity.

15. The method of claim 14 wherein said enzyme is selected from kinase, protease, peptidase, phosphodiesterase, phosphatase, dehydrogenase, reductase, carboxylase. transferase, deacetylase and polymerase.

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- 16. The method of claim 15 wherein said kinase is a protein kinase.
- 17. The method of claim 15 wherein said kinase is a serine or threonine kinase.
 - 18. The method of claim 15 wherein said kinase is a receptor tyrosine protein kinase.
 - 19. The method of claim 15 wherein said protease is a serine protease, cysteine protease or aspartic acid protease.
- 20. The method of claim 15 wherein said transferase is a 20 methyltransferase.
 - 21. The method of claim 20 wherein said methyl transferase is a cytidine methyltransferase or an adenine methyltransferase.
- 22. The method of claim 15 wherein said deacetylase is a histone deacetylase.
 - 23. The method of claim 11 wherein said carboxylase is a γ -carboxylase.
 - 24. The method of claim 15 wherein said peptidase is a zinc peptidase.

25. The method of claim 15 wherein said polymerase is a DNA polymerase.

- 26. The method of claim 15 wherein said polymerase is a RNA polymerase.
 - 27. The method of claim 12 wherein said biological activity is a membrane transport activity.
- 10 28. The method of claim 12 wherein said polypeptide is a cation channel protein, an anion channel protein, a gated-ion channel protein or an ABC transporter protein.
 - 29. The method of claim 12 wherein said polypeptide is an integrin.
 - 30. The method of claim 12 wherein said polypeptide is a Cytochrome P450 enzyme.

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- 31. The method of claim 12 wherein said polypeptide is a nuclear 20 hormone receptor.
 - 32. The method of claim 12 wherein said biological activity is a receptor activity.
- 33. The method of claim 12 wherein said receptor is a G-protein-coupled receptor.
 - 34. The method of claim 12 wherein said polypeptide is contained in a cell.
 - 35. A method for identifying an anti-neoplastic agent comprising contacting a cancerous cell with a compound found to have anti-neoplastic

activity in the method of claim 12 under conditions promoting the growth of said cell and detecting a change in the activity of said cancerous cell.

36. The method of claim 35 wherein said change in activity is a decrease in the rate of replication of said cancerous cell.

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37. The method of claim 35 wherein said change in activity is a decrease in the total number of progeny cells that can be produced by said cancerous cell.

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- 38. The method of claim 35 wherein said change in activity is a decrease in the number of times said cancerous cell can replicate.
- 39. The method of claim 35 wherein said change in activity is the death of said cancerous cell.

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40. A method for treating cancer comprising contacting a cancerous cell with an agent first identified as having gene modulating activity using the method of claim 1, 5, or 12 and in an amount effective to cause a reduction in cancerous activity of said cell.

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41. The method of claim 40 wherein said cancerous cell is contacted in vivo.

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- 42. The method of claim 40 wherein said reduction in cancerous activity is a decrease in the rate of proliferation of said cancerous cell.
- 43. The method of claim 40 wherein said reduction in cancerous activity is the death of said cancerous cell.

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44. The method of claim 40 wherein said cancer is a cancer of breast, colon, lung or prostate tissues.

45. A method for treating cancer comprising contacting a cancerous cell with an agent having affinity for an expression product of a gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 – 3049 and in an amount effective to cause a reduction in cancerous activity of said cell.

- 46. The method of claim 45 wherein said expression product is a polypeptide.
- 10 47. The method of claim 45 wherein said agent is an antibody.

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- 48. A method for monitoring the progress of cancer therapy in a patient comprising monitoring in a patient undergoing cancer therapy the expression of a gene corresponding to a polypeptide having a sequence selected from SEQ ID NO: 1 3049.
- 49. The method of claim 48 wherein said gene comprises a sequence of SEQ ID NO: 1 3049.
- 50. The method of claim 48 wherein said cancer therapy is chemotherapy.
 - 51. The method of claim 48 wherein said cancer is a cancer of breast, colon, lung or prostate tissues.
 - 52. A method for determining the likelihood of success of cancer therapy in a patient, comprising monitoring in a patient undergoing cancer therapy the expression of a gene corresponding to a polynucleotide having a sequence of one of SEQ ID NO: 1-3049 wherein a decrease in said expression prior to completion of said cancer therapy is indicative of a likelihood of success of said cancer therapy.

53. The method of claim 52 wherein said gene comprises a sequence of SEQ ID NO: 1-3049.

- 54. The method of claim 52 wherein said cancer therapy is 5 chemotherapy.
 - 55. The method of claim 52 wherein said cancer is a cancer of breast, colon, lung or prostate tissues.
- 10 56. A method for producing test data with respect to the anti-neoplastic activity of a compound comprising:
 - (a) identifying a test compound as having anti-neoplastic activity using a method of claim 12;
- (b) producing test data with respect to the anti-neoplastic activity of said test compound sufficient to identify the chemical structure of said test compound.
 - 57. A method for determining the progress of a treatment for cancer in a patient afflicted therewith, following commencement of a cancer treatment on said patient, comprising:

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- (a) determining in said patient a change in expression of one or more genes corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 3049; and
- (b) determining a change in expression of said gene compared to
 expression of said one or more determined genes prior to commencement of said cancer treatment;

wherein said change in expression indicates progress of said treatment thereby determining the progress of said treatment.

58. The method of claim 57 wherein said change in expression is a decrease in expression and said decrease indicates success of said treatment.

59. A method for determining the progress of a treatment for cancer in a patient afflicted therewith, following commencement of a cancer treatment on said patient, comprising:

(a) determining in said patient a change in expression of one or more genes corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 – 3049; and

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(b) determining a change in expression of said gene compared to expression of said one or more determined genes prior to commencement of said cancer treatment;

wherein said change in expression indicates progress of said treatment thereby determining the progress of said treatment.

60. The method of claim 59 wherein said change in expression is a decrease in expression and said decrease indicates success of said treatment.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/07748

	SIFICATION OF SUBJECT MATTER		
IPC(8)	: C12Q 1/68; C07H 21/04		
US CL	: 435/6; 536/23.1, 23.5 International Patent Classification (IPC) or to both nation	onal classification and IPC	
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Please See Co	ontinuation Sheet		
C. DOCI	JMENTS CONSIDERED TO BE RELEVANT		Relevant to claim No.
Category *	Citation of document, with indication, where ap	propriate, of the relevant passages	
X	US 5,776,683 A (SMITH et al) 07 July 1998 (07.07.1	998), especially col. 6, 25 and Table 7.	1-4
			1-4
Y	SQUIRE et al. High-resolution mapping of amplificat	ions and deletions in pediatric	14
	osteosarcoma by use of CGH analysis of cDNA micro	arrays. Genes, Chromosomes &	
	Cancer. 2003, Vol. 38, pages 215-225, especially pag	e 216 and Table 1.	
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Further	r documents are listed in the continuation of Box C.	See patent family annex.	
	Special categories of cited documents:	later document published after the intermed and not in conflict with the application by	national filing date or priority date
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/07748

Box No. II	Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)
This internat	ional search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1.	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2.	Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box No. III	Observations where unity of invention is lacking (Continuation of item 3 of first sheet)
	ional Searching Authority found multiple inventions in this international application, as follows: ontinuation Sheet
	A
1.	As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.	No required additional search fees were timely paid by the applicant. Consequently, this international search report is
Remark on 1	restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-4, with respect to the amplicon comprising chromosome 8q24.13

Form PCT/ISA/210 (continuation of first sheet(2)) (April 2005)

International application No. PCT/US05/07748

INTERNATIONAL SEARCH REPORT

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional examination fees must be paid.

Groups 1-47, claims 1-4 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing one of the 47 amplicons set forth in Table 2. For example, Group 1 is drawn to methods for identifying an antineoplastic agent by

contacting a test compound with a cell containing the 5.3 MB amplicon comprising chromosome 8q24.13. Upon election of one of the groups, please specify the amplicon to be searched.

Groups 48-3097, claims 5-9 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing one of the sequences of SEQ ID NO: 1-3049 and assaying for a change in the level of expression of one of the sequences. For example,

Group 48 is drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing SEQ ID NO: 1. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

Groups 3098-6147, claims 10-11 (in part), drawn to methods for identifying a cancerous state of a cell by assaying for the sequence of one of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

Groups 6148-9196, claims 12-34 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049 and assaying for a change in the activity of the polypeptide. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched. Further, it is noted that claim 23 has been included with this grouping because it appears that claim 23 intends to depend from claim 15, rather than claim 11.

Groups 9197-12,245, claims 35-39 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing one of the sequences of SEQ ID NO: 1-3049 and assaying for a change in the cancer cell growth of said cell. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

Groups 12,246-15,294, claims 40-47 (in part), drawn to methods for treating cancer by using a compound that effects the activity of a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the corresponding SEQ ID NO of the elected group to be searched.

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Groups 15295-18343, claims 48-55 and 57-60 (in part), drawn to methods for monitoring the progress of a cancer therapy by assaying for the level of a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

Groups 18,344-21,392, claim 56 (in part), drawn to methods for producing data comprising producing test data sufficient to identify the chemical nature of a test compound that effects the activity of a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

The inventions listed as Groups 1-21,392 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

In accordance with 37 CFR 1.475(d) Applicant is entitled to an examination of the first product, method of making said product and method of using said product. In the instant case, the first method is one which requires one of the 47 amplicons of Table 2. This product is not required for the methods set forth in the remaining groups. Thereby, Groups 48-21,392 constitute distinct groups which do not share the same corresponding technical feature of groups 1-47. Further, unity of invention exists only when there is a technical relationship among those inventions involving one or more of the same or corresponding technical features. The expression 'special technical feature" means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. The technical feature linking the claims 5-60 is the HAS2 gene. However, the HAS2 gene was known in the art at the time the invention was and thereby does not constitute a contribution over the prior art (see NCBI Database, GenBank Accession No. U54804). Accordingly, there is no special technical feature linking the recited groups, as would be necessary to fulfill the requirement for unity of invention.

It is also noted that each of the present claims has been presented in improper Markush format, as distinct methods are improperly joined in the claims. Each amplicon of Table 2 and each nucleic acid sequence of SEQ ID NO: 1-3049 is structurally and functionally distinct from and has a different special technical feature than each other the amplicons and nucleic acid sequences. The chemical structure of each amplicon and nucleic acid sequence differ

from each other. For example, a polynucleotide comprising SEQ ID NO: 1 is chemically, structurally, and functionally different from a molecule comprising SEQ ID NO: 2. Given the differences in the structure, function and effect the amplicons of Table 2 and the sequences of SEQ ID NO: 1-3049, these compounds are not considered to share a special technical feature as would be necessary to fulfill the requirement for unity of invention. These distinct compounds do not have both a "common property or activity" and a common structure as would be required to show that the inventions are "of a similar nature." As the products and methods encompassed by the claims do not share a special technical feature, the distinct products and methods may not properly be presented in the alternative. Accordingly, the claims have been separated into a number of groups corresponding to the number of different inventions encompassed by the claims, and the claims will be searched only as they read upon the invention of the elected group

Additionally, each of the claimed methods have different objectives and require different process steps. The methods of claims 1-4 require cells containing one of the amplicons of Table 2 and requires assaying for a change in the amplification ratio of the amplicon. The methods of claims 5-9 require the use cells that contain one of the sequences of SEQ ID NO: 1-3049, and requires assaying for a change in gene expression by assaying for mRNA or protein levels in order to

accomplish the objective of identifying a antineoplastic agent. The methods of claims 10-11 require assaying for the level of one of the sequences of SEQ ID NO: 1-3049 in order to accomplish the objective of identifying a cancerous state of a cell. The methods of claims 12-34

require contacting a cell with a test agent and assaying for a change in biological activity of a polypeptide encoded by SEQ ID NO: 1-3049. The methods of claims 35-39 require contacting a cell with a test compound and assaying for the cancerous state of a cell. The methods of

claims 40-47 require administering an agent to an individual in order to accomplish the objective of treating cancer. The methods of claims 48-55 and 57-60 require determining gene expression levels of a polypeptide of one of SEQ ID NO: 1-3049 and assaying for polypeptide levels in order to accomplish the objective of monitoring the progress of cancer therapy. The method of claim 56 requires identifying test compounds that have

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antineo plastic activity and producing test data in order to obtain sufficient data to identify the chemical structure of the test compound. In addition to differences in objectives, effects, and method steps, it is again noted that the claims of the present Groups are not directed to the detection or identification of molecules having the same or common special technical feature, for the reasons discussed above.
Continuation of B. FIELDS SEARCHED Item 3: WEST: USPT, JPAB, EPAB, DWPI, PGPUB; DIALOG: MEDLINE, CA, BIOSIS, EMBASE search terms: 8q24.13, 8q24.1; amplification or amplified or copy number; cancer or tumor or neoplasm